Remission of Severe Neonatal Diabetes With Very Early Sulfonylurea Treatment

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Mutations in *KCNJ11* and *ABCC8* can cause neonatal diabetes mellitus (NDM) (1) that may respond to sulfonylureas (2).

We report three NDM infants treated with glyburide very early in life who were able to maintain good glycemic control with minimal dosing.

CASE 1

This 6-year-old male (Case-1-male) was previously reported at birth (3). Mother and sister (Case-1-female) both had NDM and were given insulin for 24 and 6 years, respectively, then treated with high-dose glyburide; mother still requires some insulin. Case-1-male had NDM at 3 days and was given glyburide 0.2 mg/kg/day, weaned to 0.05 mg/kg/day, and maintained normal hemoglobin A_{1c} for 5 years (Fig. 1*A*) continuing glyburide 0.075 mg thrice daily (mixing a crushed 5 mg tablet with 10 cc water, giving 0.15 cc for each dose, 0.012 mg/kg/day). All had a heterozygous mutation in *KCNJ11* (R201H).

CASE 2

A boy with hyperglycemia (125–247 mg/dL) (6.9–13.7 mmol/L) at 3 days old was given glyburide 0.2 mg/kg twice daily on day 6 and weaned to 0.05 mg/kg/day by day 10 (Fig. 1*B*). Mother and maternal uncle and aunt, diagnosed with diabetes at age 15, 10, and 8 years, respectively, take insulin. The infant and mother had heterozygous mutation in *ABCC8* (c1463C>T [p.Thr488Ile]); these results were not available until day of life 37. Mother has been weaned off insulin to glyburide 2.5 mg thrice daily.

CASE 3

A girl, 27 weeks' gestation, with hyperglycemia at 3 days old (Fig. 1*C*), was started on an insulin infusion. On day 20, she was given glyburide 0.1 mg/kg twice daily, later reduced to 0.04 mg/kg twice daily, and insulin was discontinued. At 1 month, glyburide was stopped for necrotizing enterocolitis. Good glycemic control continued without glyburide or insulin: hemoglobin A_{1c} was 4.6% (27 mmol/mol) after 1 year. Genetic testing obtained later identified the same *ABCC8* mutation as in the unrelated Case 2. Parents have no history of diabetes.

CONCLUSIONS

These outcomes suggest that functional β-cells may be preserved with low doses of sulfonylurea started very early in life without insulin administration or risk of severe hypoglycemia. This is consistent with murine data indicating that early treatment with sulfonylureas preserves β-cells in K_{ATP}-dependent diabetes (4).

These low doses of glyburide are consistent with an infant reported with hyperglycemia at 2 days, placed on glyburide on day 7, and successfully treated using 0.02 mg/kg/day (5). In these cases, genetic testing was delayed due to birth in a country without quick access to testing, refusal of insurance coverage, or extreme prematurity. Khurana et al. (5) suggested that "patients with the onset of diabetes prior to 1 year of age who have a strong family history of early-onset diabetes" receive a trial of sulfonylurea even without genetic testing.

We extend this recommendation to suggest that a trial of sulfonylurea be immediately given in all cases of diabetes diagnosed in the first weeks of life. Very early sulfonylurea treatment may prevent progression to severe NDM and preserve sufficient glucose-modulated insulin secretion to render the diabetes mild and reduce acute and long-term complications.

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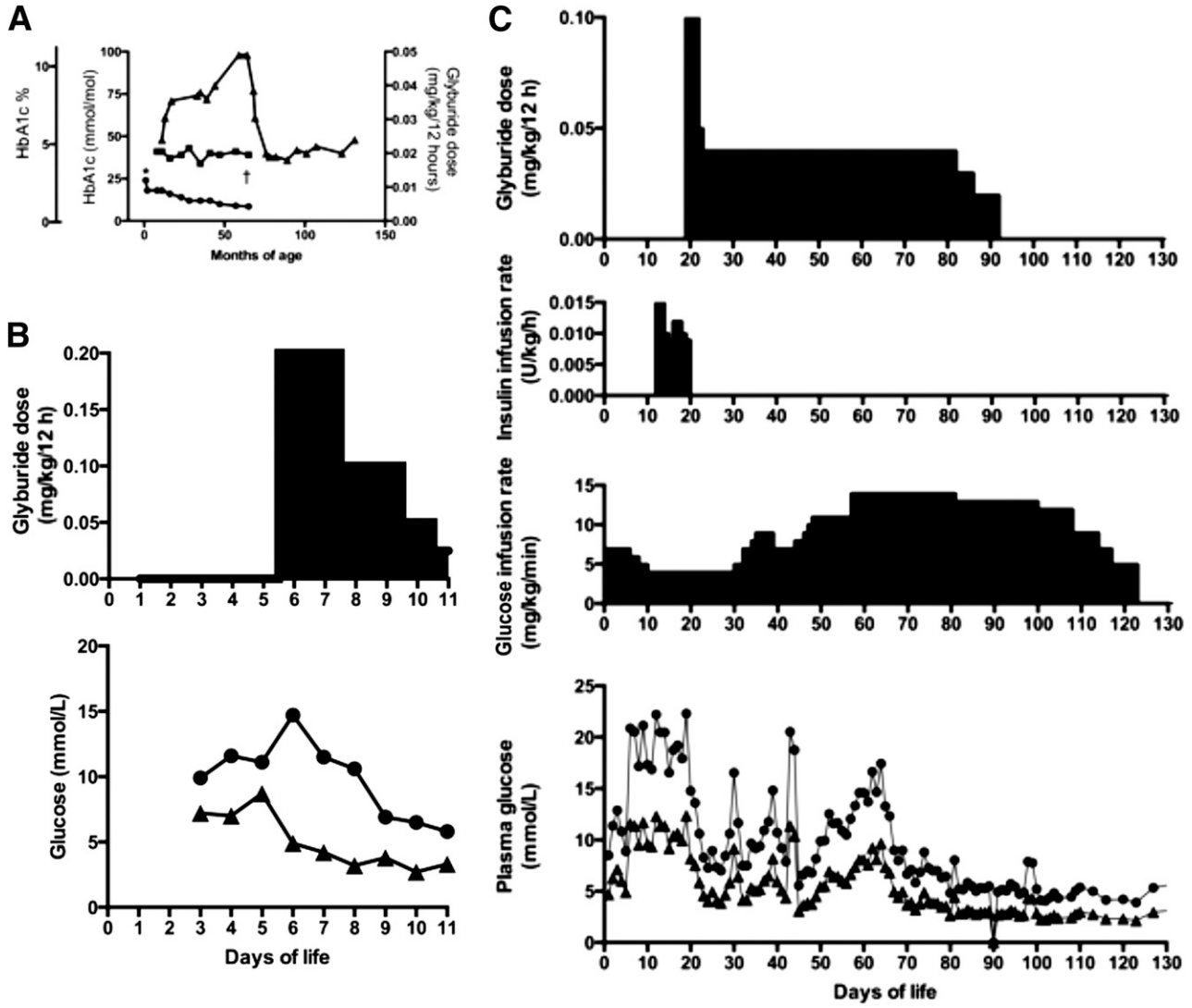

Figure 1—*A*: Hemoglobin A_{1c} (% and mmol/mol) in Case-1-male (squares) and Case-1-female (triangles) and glyburide dose (mg/kg/12 h) of Case-1-male (circles) during the months of age indicated. The asterisk and cross mark the age at which glyburide was initiated in Case-1-male and Case-1-female, respectively. *B*: Dose of glyburide (mg/kg/12 h) and plasma glucose (mmol/L) in the first 11 days of life in Case 2. The highest plasma glucose concentration of each day is shown by the circles, the lowest by the triangles. *C*: Glyburide dose (mg/kg/12 h), intravenous insulin infusion rate (U/kg/h), intravenous glucose infusion rate (mg/kg/min), and plasma glucose (mmol/L) in the first 130 days of life of Case 3 (circles are highest plasma glucose concentration per day, triangles are lowest).

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