Permanent neonatal diabetes by a new mutation in KCNJ11: unsuccessful switch to sulfonylurea

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SUMMARY

Permanent neonatal diabetes (PNDM) can result from activating heterozygous mutations in KCNJ11 gene, encoding the Kir6.2 subunit of the pancreatic ATP-sensitive potassium channels (K<sub>ATP</sub>). Sulfonylureas promote K<sub>ATP</sub> closure and stimulate insulin secretion, being an alternative therapy in PNDM, instead of insulin. Male, 20 years old, diagnosed with diabetes at 3 months of age. The genetic study identified a novel heterozygous mutation in exon 1 of the KCNJ11 gene – KCNJ11:c.1001G>C (p.Gly334Val) – and confirmed the diagnosis of PNDM. Therefore it was attempted to switch from insulin therapy to sulfonylurea. During glibenclamide institution C-peptide levels increased; however, the suboptimal glycemic control lead us to restart an intensive insulin scheme. This new variant of KCNJ11 mutation had a phenotypic lack of response to sulfonylurea therapy. Age, prior poor metabolic control and functional change of K<sub>ATP</sub> channel induced by this specific mutation may explain the observed unsuccessful switch to sulfonylurea. Interestingly, C-peptide levels raise during glibenclamide administration support some degree of improvement in insulin secretory capacity induced by the treatment. Understanding the response to sulfonylurea is crucial as successful treatment may be life-changing in these patients.

INTRODUCTION

Permanent neonatal diabetes mellitus (PNDM) is a rare form of diabetes with an estimated prevalence at 1 in 252,000 (1). It is characterized by the onset of diabetes before the age of 6 months, being a permanent condition that does not go into remission. This form of diabetes can be caused by variants of several genes, including KCNJ11, ARCC8, GCK, and IPF1 gene (2). Approximately half of the cases are caused by a mutation in KCNJ11, which encodes the Kir6.2 subunit of the pancreatic ATP-sensitive potassium channels (K<sub>ATP</sub>) (3); the majority of these patients develop isolated PNDM, but 20% have associated neurologic disturbances like DEND syndrome, characterized by developmental delay, epilepsy, and neonatal diabetes (3).

K<sub>ATP</sub> channel is a key regulator of beta-cell insulin secretion. In the pancreatic beta cell, the intracellular increase of ATP, due to glucose metabolism, leads to K<sub>ATP</sub> channels closure, which causes membrane depolarization and opening of voltage-gated Ca<sup>2+</sup> channels; this Ca<sup>2+</sup> influx can trigger insulin release (4).

Activating KCNJ11 mutations are associated with diabetes: these mutations cause an inappropriate activation of K<sub>ATP</sub> channel channels, which fail to close in response to an increase in plasma glucose levels, leading to insulin secretion dysfunction (5,6). The identification of Kir6.2 (KCNJ11) mutations has critical therapeutic implications, since sulfonylureas, a class of oral anti-diabetic agents, act through that channels (7). Sulfonylureas are able to promote K<sub>ATP</sub> channels closure by an ATP-independent route, thereby stimulating insulin secretion in those patients (8). Thus, sulfonylureas may represent a suitable therapy for patients with KCNJ11 mutations, instead of insulin therapy.

CASE REPORT

A caucasian male, son of non-consanguineous healthy parents, was born by a dystocic parturition (forceps) at 36 weeks of gestation. Prenatal history was remarkable for intrauterine growth restriction. The birth weight was 1800 g (< 3<sup>rd</sup> centile), length 44 cm (10<sup>th</sup> centi-
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Abstract

permanent forms of diabetes presented before 6 months raise the clinical suspicion of PNDM. The identification of the genetic etiology in this form of diabetes has important clinical implications, since sulfonylureas may have double benefits in PNDM, comparing to insulin therapy: promotion of a global improvement in glycemic control, causing reduction in blood glucose fluctuations; and, consequently, risk reduction of diabetic complications and improvement of quality of life of the affected patients (11,12).

Although sulfonylureas seem highly effective and safe in the treatment of the majority of patients, not all respond. This case represents an unsuccessful example of transition from insulin therapy to sulfonylurea. Therefore it is important to reflect about the possible associated reasons, which may justify the unsuccessful switch. Firstly, the attempt to withdrawal insulin treatment began at an adult age and after a long period of poor glycemic control (HbA1c 8-12.5%). Age and poor metabolic control seem to be important predictors of sulfonylureas responsiveness, since an effective transfer is less likely in older patients, with worse glycemic control (13,14). In addition, starting sulfonylureas treatment at later age is associated with increased dose requirement. Although the roles of age and glucose homeostasis are not completely understood, some elegant studies in mouse models might further expand our knowledge: mice with uncontrolled diabetes had less functioning beta cells, comparing to those treated with insulin therapy, whose beta cells were preserved (15). So, poor long-term glucose control, enhanced in older patients, may result in decline and impairment of beta cells function, which may further explain the lack of response to sulfonylureas.

Secondly, the functional properties of $K_{ATP}$ channel predict the clinical response to sulfonylurea therapy observed in these patients (8). It was shown that tolbutamide treatment blocked more than 75 percent of the $K_{ATP}$ channel in patients carrying $KCNJ11$ mutations that had clinical response to sulfonylureas. In contrast, patients who failed to respond had less than 65 percent blockage with tolbutamide (8). Thus, the channel changes induced by this specific novel variant of $KCNJ11$ gene, a mutation on c1001G>7 (p.Gly334Val), may also explain the observed reduction in drug sensitivity. However, it is important to notice the rise in C-peptide levels during glibenclamide administration, which may reflect a partial improvement in the insulin secretory capacity induced by the treatment. Thus, we might
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speculate that the changes on K\textsubscript{ATP} channel induced by this novel variant on KCNJ11 might not be irreversible and may respond to sulfonylureas, mainly if the attempt to switch from insulin can be achieved early in life and the patient has prior good glycemic control.

We report, for the first time, the heterozygous mutation KCNJ11:c1001G>T (p.Gly334Val) in exon 1 of the KCNJ11 gene, in a patient with permanent neonatal diabetes mellitus. This case highlights the clinicians to consider a neonatal form of diabetes if diagnosis is made up within six months of life. The identification of this form of diabetes may be life-changing, mainly if sulfonylurea treatment could be well-succeed in early life.

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**REFERENCES**


