Neonatal diabetes mellitus due to L233F mutation in the *KCNJ11* gene

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Background: **Neonatal diabetes mellitus (NDM) due to *KCNJ11* gene mutation presents with diabetes in the first 3 months of life and sometimes with neurological features like developmental delay, muscle weakness and epilepsy.**

Methods: **A 5-week-old boy presented with diabetic ketoacidosis. Molecular genetic analysis of the patient revealed heterozygous missense mutation, L233F in the *KCNJ11* gene, while his mother was mosaic for the same mutation.**

Results: **The treatment strategy was changed from insulin injections to oral glibenclamide and with a better glycemic control.**

Conclusion: **The patient with NDM due to mutation L233F (not reported till date) in the *KCNJ11* gene can be successfully treated with oral glibenclamide therapy.**

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Introduction

Neonatal diabetes mellitus (NDM) usually presents itself within the first 3 months of life and is either transient or permanent. It requires lifelong insulin therapy.[1] Heterozygous gain of function mutations in the *KCNJ11* gene encoding Kir 6.2, the pore forming subunit of the ATP-sensitive K^+ channel (K^+ ATP channel), is the most common cause of NDM which can be treated with oral sulfonylureas.[2] We report a 5-week-old boy with NDM caused by a mutation (L233F) in the *KCNJ11* gene, who was successfully treated with oral glibenclamide.

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Case report

A 5-week-old boy presented with fever, polyuria since 3 days after birth. He was febrile, dehydrated and had acidotic breathing when referred to our hospital. He had a birth weight of 2.25 kg (<10 th percentile) and the perinatal period was uneventful. His weight was 3.25 kg, length 50 cm and head circumference 37 cm. Laboratory investigations revealed high blood glucose level of 600 mg/dL and severe ketoacidosis (blood pH 6.9, HCO_3^- 2.4 mmol/L; urine positive for ketones and sugar). He had a low C-peptide level of 0.16 ng/dL (normal: 0.9-7.1 ng/dL). Molecular genetic analysis revealed the patient was heterozygous for a missense mutation, L233F, in the *KCNJ11* gene. This C>T mutation at nucleotide 697 (c.697 C>T) resulted in the substitution of phenylalanine for leucine at codon 233 (p. Leu233Phe) confirming a diagnosis of neonatal diabetes due to a mutation in the Kir 6.2 subunit of the KATP channel. His mother was mosaic for the same mutation and the level of mosaicism was estimated at 20% within her lymphocyte DNA. However she was asymptomatic and had normal blood glucose level. His father did not carry any mutation.

The patient was treated with intravenous regular insulin. On this he developed episodes of hypoglycemia, so was shifted to neutral protamine haegdorn (NPH) insulin 1.3 U/kg per day in 2 divided doses, following which no episodes of hypoglycemia were recorded. The patient was subsequently started on oral glibenclamide at 0.1 mg/kg at a single dose in the morning simultaneously along with NPH insulin. On the third day, glibenclamide (0.1 mg/kg) was given 12 hourly with an evening NPH insulin dose reduced by half. On the fifth day, the morning dose of glibenclamide was increased to 0.2 mg/kg and the morning dose of NPH insulin ommitted. After another 2 days, glibenclamide was given at a dose of 0.2 mg/kg 12 hourly. During this shift, blood glucose was monitored. After 10 days, the patient did not require any insulin. He was now 7 months old with a good glycemic control while on oral glibenclamide (0.4 mg/kg per day). His HbA1C improved from 7.5% (pre-glibenclamide) to 5.2% (post-glibenclamide) without any episodes of hypoglycemia.

Discussion

Gloyn et al[1] has reported several families with heterozygous activating mutations in Kir 6.2 leading to NDM. Few mutations were inherited in an autosomal dominant inheritance with no imprinting effect with the majority (80%) occurring *de novo*. There is a clear genotype-phenotype relationship for Kir 6.2 mutations.[1-3] Mutation at position 201 in gene encoding Kir 6.2 is associated with NDM while mutations at position V59M and V59G are associated with neurological abnormalities like developmental delay, muscle weakness, epilepsy and in some cases dysmorphism in addition to NDM. Mutations causing NDM alone impair ATP sensitivity directly (at the binding site), whereas those associated with severe diseases act indirectly by biasing the channel conformation toward the open state.[3] In the *KCNJ11* gene, a total of 63 mutations have been reported in families with hyperinsulinism, permanent and transient NDM and developmental delay, epilepsy and neonatal diabetes (DEND).[4] The L233F mutation found in our patient is not reported to date. This seems to be a mutation causing NDM only as the patient does not have any neurological abnormalities or dysmorphism. The probable mechanism by which the *KCNJ11* gene mutation caused NDM in our patient is by impairing ATP-dependent channel inhibition without much changes in the fraction of time the channel remains open in the absence of ATP (the intrinsic open probability). Intrauterine growth restriction found in the patient is likely due to reduced insulin secretion *in utero*.

Knowing the genetic etiology of NDM has revolutionized therapy as patients with Kir 6.2 mutations can be successfully switched from insulin injections to oral sulphonylureas.[5,6] K^+ ATP channels that are insensitive to ATP as a consequence of Kir 6.2 mutations can still be closed by sulphonylureas that bind to the SUR subunit and close the channel directly. The pediatric patients require high doses of sulphonylureas: e.g., 0.4-1 mg/kg per day glibenclamide compared with a maximum suggested dose of 0.33 mg/kg for a 60-kg adult with type 2 diabetes.[2] Mutations that cause neurological symptoms are less sensitive to inhibition by sulfonylurea, which may require even higher doses. Our patient has normal growth with oral glibenclamide at a dose of 0.4 mg/kg per day. Home monitoring of blood glucose daily on glucometer showed a better glycemic control than on insulin therapy. Monitoring of full blood count and liver functions should be done on therapy. The common side effects are skin allergies, diarrhea, cholestatic jaundice, elevated liver enzymes and hematological-anemia, leucopenia and thrombocytopenia.

The presence of mutation in the mother's leukocyte DNA is consistent with a post-zygotic mutation occurring early in embryonic development. The mutation will also be present in the germ cells though it is not possible to measure the mutation load and hence the risk to future siblings. However, if the mutation arose early enough to affect all primordial germ cells, the recurrence risk could be up to 50% for each pregnancy.[7]

In view of increased risk of NDM compared to population, parents of children with *KCNJ11* mutations should be offered molecular genetic testing for future siblings at birth. Cord blood should be tested for the mutation and if identified, blood glucose should be monitored so as to diagnose diabetes early.

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