

## Case Report

# Permanent Neonatal Diabetes in a Patient with a *KCNJ11*/Q52R Mutation Accompanied by Intermittent Hypoglycemia and Liver Failure

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Received 7 May 2009; Revised 12 July 2009; Accepted 16 July 2009

Recommended by Michel Polak

The most common monogenic cause of neonatal diabetes is mutation in *KCNJ11*, which encodes a potassium channel in pancreatic beta cells. Some mutations in this gene, including Q52R, have been described in association with neurological deficits, but never with hepatic involvement. We report the second case of neonatal diabetes in a patient with a *KCNJ11*/Q52R mutation. This patient's clinical course did not include obvious neurological deficits despite the presence of prematurity, but did include transient hyperbilirubinemia, and recurrent hypoglycemia. The phenotypic spectrum of *KCNJ11* mutations is variable and is likely influenced by additional genetic and environmental factors.

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## 1. Introduction

Neonatal diabetes mellitus (NDM) is a rare monogenic disorder that presents as hyperglycemia, failure to thrive, or diabetic ketoacidosis in the first 6 months of life [1]. The permanent form of NDM is most commonly caused by a mutation in *KCNJ11*, the gene encoding the Kir6.2 subunit of the ATP-sensitive potassium channel. Kir6.2 assembles with SUR to form potassium channels in the beta cell, brain, heart, and muscle [1].

More than thirty mutations in *KCNJ11* have been identified [2]. Those mutations producing the most profound reduction in ATP sensitivity are associated with the most severe phenotype known as DEND syndrome (developmental delay, epilepsy, and NDM). A single patient with DEND harboring a Q52R mutation (c.155A>G) of *KCNJ11* was reported in 2004 [3] (referred to as ISPAD 27), and his clinical course has been described by Sumnik et al. [4]. This patient was initially diagnosed with type 1 diabetes in the first week of life and treated with insulin. When his mutation was discovered at age 4, he was given a trial of glibenclamide but showed no response. He is currently 9 years old and has severe developmental delay and epilepsy.

Herein we describe a second case of a patient with a Q52R mutation in *KCNJ11*. In addition to NDM, his clinical course was notable for prematurity, severe hyperbilirubinemia and intermittent hypoglycemia unrelated to his diabetes treatment, features that have not been described in any other children with NDM. Notably, he did not have any obvious neurological deficits.

## 2. Case Report

Baby Boy SM was the 930 g product of a 26.5-wk dichorionic twin gestation to a 28 year-old G<sub>3</sub>P<sub>0</sub> mother conceived by in vitro fertilization. At birth, he suffered from respiratory distress and hypotension. His initial blood glucose was 4.8 mmol/L, but when switched from oral to parenteral nutrition (at a glucose infusion rate of 3.6 mg/kg/min) on day of life 2, his blood glucose rose to greater than 11 mmol/L (Figure 1).

Consistent with a diagnosis of diabetes, his insulin and C-peptide levels were inappropriately low (6.3 pmol/L and 0.07 nmol/L, resp.) at a time of hyperglycemia (12.3 mmol/L). He required several insulin boluses during the

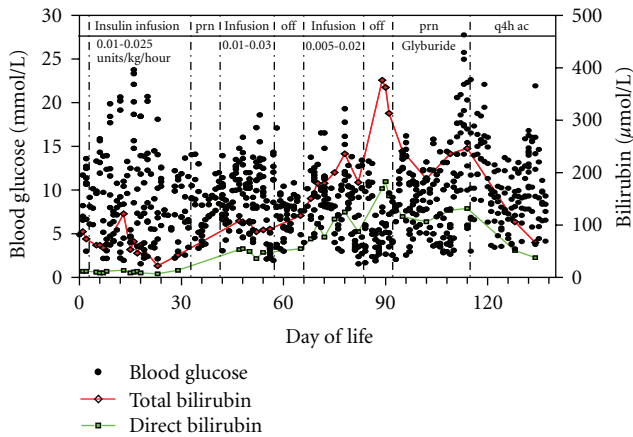


FIGURE 1: Serum glucose, total and direct (conjugated) bilirubin levels from birth to 3 (1/2) months of age. Treatment of hyperglycemia detailed above graph. Insulin infusion doses expressed in units/kg/hour.

TABLE 1: Laboratory evaluation of patient SM to determine etiology of hypo- and hyperglycemia.

Analyte	Patient	Normal value
Insulin (pmol/L)		
at blood glucose 12.3 mmol/L	6.3	21–136 (fasting)
at blood glucose 1.7 mmol/L	<1.4	21–136 (fasting)
C-peptide (nmol/L)		
at blood glucose 12.3 mmol/L	0.07	0.3–1.2 (fasting)
Hb <sub>A1C</sub> at 3 mo (%)	5.7	4–6
Pancreatic auto-antibodies (U/L)		
GAD	0.64	<0.1
IA2	0.05	<0.1
Cortisol (nmol/L)		
baseline	85.5	
after 62.5 mcg cortosyn	717.3	>552
IGF-1 (nmol/L)	<3.3	3.3–32
IGFBP-3 (mg/L)	0.9	1.4–4.4
Free thyroxine (pmol/L)	11.6	10.3–23.2

first week of life, and a constant infusion of regular insulin (at 0.05 units/kg/hour) was started on day of life 7. As detailed in Figure 1, his requirement for insulin was extremely variable. He frequently transitioned from hyper- to hypoglycemia despite careful titration of his insulin infusion and hourly blood glucose measurements. When he became hypoglycemic, insulin was discontinued, often for several days, until his blood glucose again rose above 11 mmol/L. He was not consistently on insulin until 3 months of age. His normal Hb<sub>A1C</sub> (Table 1) likely reflects this variability, but may also be falsely low due to his requirement for red blood cell transfusions in the setting of liver failure (described hereafter).

Because of the presentation of diabetes in the neonatal period, he was tested for monogenic causes of neonatal

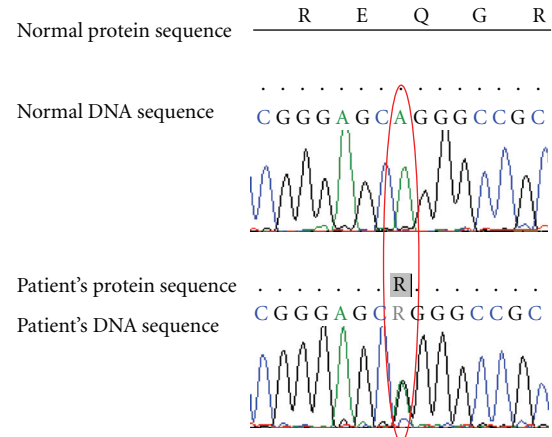


FIGURE 2: DNA sequence of *KCNJ11* from the patient. Substitution of G for A at nucleotide 155 (c.155A>G) results in Arginine (R) instead of Glutamine (Q) at amino acid 52 (Q52R).

diabetes. He tested negative for chromosome 6 uniparental disomy as well as for mutations in glucokinase and insulin promoter factor 1. He was also found to have a normal proinsulin level (4.1 pmol/L). Further testing, however, revealed a heterozygous mutation in the *KCNJ11* gene (c.155A>G, Q52R, Figure 2) which was not present in his parents or twin sister. He also had a normal karyotype. His clinical course and diagnostic studies strongly supported the diagnosis of NDM; however, his recurrent hypoglycemia was perplexing. Although a single low insulin level (<1.4 pmol/L) at a time of hypoglycemia (1.7 mmol/L) suggested that factors other than insulin were involved (Table 1), it is still possible that he had intermittent bursts of insulin secretion which were undetected due to insulin's short half-life. Because *KCNJ11* mutations that cause NDM sometimes respond to sulfonylurea treatment, at 14 weeks of age, glipizide was added to his insulin therapy at 0.15 mg/kg/day and increased to 0.75 mg/kg/day over a 4-day period. Upon initiation of glipizide treatment, his insulin dose was halved (0.03 to 0.015 units/kg every 3 hours as needed for blood glucoses > 11 mmol/L), and he required one to three insulin injections per day (Figure 1). Due to diarrhea and weight loss (195 g which represents nearly 10% of initial body weight), the medication was discontinued after 10 days. He was managed solely with insulin thereafter, and at discharge he required 0.3 units/kg/day of Lispro prior to each meal.

At 2 months of age (corrected age 34.5 weeks), the patient developed liver dysfunction (Figure 1, Table 2). Of note, at this time he had been off of parental nutrition for over one month. His ALT and AST both rose to over 200 IU/L, his total bilirubin peaked at 376.2 μmol/L (direct bilirubin 169.3 μmol/L), and he required several doses of fresh frozen plasma to treat a coagulopathy (PTT > 150 seconds). The etiology of his liver failure was never found despite an exhaustive laboratory evaluation. He had a normal lipase and alpha-1-antitrypsin level, and his newborn screen was

TABLE 2: Laboratory evaluation of patient SM to determine etiology of liver failure.

Analyte	Patient	Normal value
ALT (IU/L)*	266	0–54
AST (IU/L)*	424	16–74
Alkaline Phosphatase (IU/L)*	866	40–300
Gamma-glutamyl transpeptidase (IU/L)*	122	1–78
Bilirubin, total ( $\mu\text{mol/L}$ )*	376.2	2–17
Bilirubin, direct ( $\mu\text{mol/L}$ )*	169.3	<14
Lipase (IU/L)	8	3–60
Alpha-1-antitrypsin ( $\mu\text{mol/L}$ )	24	16–37
PT (s)*	20.5	12.2–14.8
PTT (s)*	>150	23.8–36.6
Albumin (g/L)	31	29–48
Total Protein (g/L)	42	44–75
Hepatitis Panel (B, C)	NEG	NEG
Newborn Screen for Cystic Fibrosis	NEG	NEG

\* Peak value measured.

negative for cystic fibrosis. Hepatitis B core and surface antigen and antibody, hepatitis B e antigen, and hepatitis C antibody were all undetectable, but he had a strongly positive anti-GAD titer, which may have represented a cross-reaction with a hepatitis antigen (Table 1) [5]. He had no evidence of adrenal insufficiency and was euthyroid. He was growing well but his IGF-1 and IGFBP-3 levels were low, likely secondary to impaired synthesis by his compromised liver (Table 1). Two liver ultrasounds were normal, and a liver biopsy showed diffuse, toxic/metabolic injury thought to be a secondary process. With supportive treatment and time, his liver function improved.

At approximately 3 months of age (corrected age 37 weeks), the patient underwent a formal neurodevelopmental assessment. Despite his preceding critical illness, he demonstrated normal passive range of motion of all extremities, a strong grasp and suck, and was able to fixate on and scan faces and bring his hands to his mouth. The only deficit noted was a decrease in his spontaneous motor activity. By the time of discharge, at age 4 months of age (corrected age 2.5 weeks), however, he had achieved the same developmental milestones as had his healthy twin sister.

A diabetes nurse educator taught the patient's parents how to administer insulin and to use a glucometer on several occasions prior to discharge. He saw his pediatrician the day of discharge and appeared well but died unexpectedly in the middle of the night. There was no obvious cause of death and no autopsy was performed.

### 3. Discussion

This report describes the unique phenotype of the second patient with NDM secondary to a Q52R mutation in *KCNJ11*. Unlike other patients with NDM, our patient had intermittent hypoglycemia (in addition to hyperglycemia),

even when not being treated with insulin. Our patient was clearly at risk for hypoglycemia due to reduced hepatic glycogen stores associated with prematurity and liver disease. If these were the only contributing factors, however, one would expect his hypoglycemic episodes to have clustered early in the neonatal period, during periods of severe liver dysfunction, and with longer episodes of fasting. This is not the pattern depicted in Figure 1: his liver failure was progressive rather than episodic, he was prone to hypoglycemia before his bilirubin rose and after it returned to normal, and his hypoglycemia occurred both with fasting and after a meal.

Our patient was also unique in having idiopathic liver failure. Liver involvement has not been described in any patient with NDM, including ISPAD27. The majority of NDM patients, however, have not been vulnerable premature neonates subject to the same physiologic stressors as our patient, so the liver disease may have been solely related to factors associated with prematurity including hypoperfusion, infection, hypoxia, or drug effects. However, it is also possible that a *KCNJ11* mutation increases one's susceptibility to liver failure but is only manifested in combination with other factors related to prematurity. As noted previously, Kir6.2 is widely expressed and has been detected in human liver cell lines [6], but its potential function in the liver has not been explored.

In summary, this patient represents the second reported case of NDM secondary to a Q52R mutation in *KCNJ11* and the first report of NDM accompanied by hypoglycemia and liver failure. This patient's normal neurodevelopment, at least until 4 months (corrected age 2.5 weeks), was also unexpected given that the only other patient reported with NDM and this *KCNJ11* mutation has DEND. Because the pathogenesis of developmental delay and epilepsy in DEND patients remains unknown, we believe that clinicians taking care of patients with NDM should carefully evaluate them for intermittent hypoglycemic insults as well as liver dysfunction.

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