First case of neonatal diabetes with \textit{KCNJ11} Q52R mutation successfully switched from insulin to sulphonylurea treatment

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**Keywords**

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**ABSTRACT**

In this report, we present the first known case of intermediate developmental delay, epilepsy and permanent neonatal diabetes (DEND) syndrome caused by a Q52R mutation in the \textit{KCNJ11} gene who was successfully switched (at age 1.3 years) to sulphonylurea monotherapy, namely glibenclamide. The most recent evaluation, after 2 years, showed a glycated hemoglobin level of 6.0% (42 mmol/mol). This mutation is so severe that none of the previously reported four cases were able to switch from insulin to sulphonylurea monotherapy. The Q52R mutation seems to have a chance of positive response to glibenclamide administered every 3–6 h instead of the classical 8–12 h, in doses around or above 2.5 mg/kg/day.

**INTRODUCTION**

Developmental delay, epilepsy and permanent neonatal diabetes (DEND) syndrome represents the association of developmental delay and epilepsy, which is usually diagnosed within the first 12 months of life, and permanent neonatal diabetes\(^1\). Some patients do not develop epilepsy, and they are classified as having intermediate DEND syndrome. The Q52R mutation in the \textit{KCNJ11} gene encoding for the inward-rectifier (Kir) 6.2 subunit of the adenosine triphosphate (ATP)-sensitive potassium channel is responsible for rare, but severe, cases of DEND syndrome\(^2\). This mutation is so severe that none of the four previously reported cases was able to switch from insulin to sulphonylurea monotherapy\(^2\)–\(^5\). One of the patients died relatively soon after the diagnosis, whereas the others had important developmental delay while continuing on insulin, with one case on combined treatment of insulin and sulphonylurea\(^2\)–\(^5\).

In the present report, we present the first known case of intermediate DEND syndrome caused by the Q52R mutation in the \textit{KCNJ11} gene, who was able to completely switch from insulin to sulphonylurea monotherapy, namely glibenclamide.

**CASE REPORT**

Baby AM, a boy, was born at 40 weeks of gestation as the third child in a non-consanguineous family. He weighed 2,550 g at birth, and after the delivery at home, both the newborn and his mother were admitted to a local hospital with maternal–fetal infection and respiratory distress syndrome. He was transferred to a tertiary hospital after 2 weeks because of neonatal sepsis and prolonged neonatal jaundice. Here, at approximately 3 weeks of age, a blood glucose value of 359 mg/dL (19.9 mmol/L) was found for the first time, accompanied by glycosuria (1,000 mg/dL), but no ketonuria. He received insulin treatment (2 U detemir twice daily, weight unavailable) for just 4 days, followed by apparent full remission of high blood glucose values until the age of 6 weeks, as shown by venous blood glucose measurements. He restarted insulin treatment (2 U detemir twice daily, weight unavailable) for just 4 days, followed by apparent full remission of high blood glucose values until the age of 6 weeks, as shown by venous blood glucose measurements. He restarted insulin treatment (detemir, dose unavailable) at starting age 6 weeks (high blood glucose relapse), followed by the addition of glibenclamide at age 8 weeks, and glibenclamide only at hospital discharge at age 14 weeks (0.6 mg/kg/day), although at discharge fasting blood glucose was still relatively high (9.2 mmol/L / 165 mg/dL). No genetic analysis was carried out at that time. In addition, islet cells, glutamic acid decarboxylase 65 and tyrosine phosphatase antibodies were measured and were all negative. The patient was readmitted to hospital 2 weeks later because of high fever as a result of a respiratory infection, and insulin (2 U detemir...
in the morning, weight unavailable) was again added to glibenclamide, as blood glucose values showed important fluctuations (glycated hemoglobin [HbA1c] 7%; 53 mmol/mol). Unfortunately, he returned after 1 month (age 18 weeks) with severe ketoacidosis while on combined insulin and glibenclamide treatment, and has since been treated with insulin alone. Informed consent was obtained from the mother, including for article publication. Approval was also obtained from the 'Elias' Hospital Ethics Committee.

The patient was admitted to 'Elias' University Emergency Hospital, Bucharest, Romania, at age 1.3 years for a scheduled attempt to switch to glibenclamide, after the genetic evaluation (Exeter laboratory) showing the presence of a de novo p.Q52R missense mutation in the KCNJ11 gene. This was the first admission to our hospital, as all previously described history was from medical supervision carried out in another tertiary hospital. He had a low normal length (75 cm, 10th centile) and a high normal weight (13 kg, 93rd centile), that combined with muscle hypotonia and severe neurodevelopmental delay gave the impression of a giant 4-month-old infant, with a mild umbilical hernia. He was resting on his back most of the time, unsuccessfully trying to roll over, and he could not stay on his buttocks without external support. He spoke sounds, but no syllables. He did not yet tolerate any foods, except for an age-related milk formula. No seizure episode was encountered so far. HbA1c was 9.4% (80 mmol/mol) and C-peptide 0.02 ng/mL, with otherwise normal biochemistry, including liver tests and lipid profile, normal thyroid stimulating hormone, triiodothyronine, free thyroxine, anti-thyroid peroxidase antibodies, insulin-like growth factor 1, and insulin-like growth factor 1 binding protein 3. Glibenclamide was given in small portions in a rapidly escalating dose to approximately 0.8 mg/kg/day, with finger stick and continuous glucose monitoring system glucose values dropping to a near normal range within 9 days (Figure 1). Besides at baseline, insulin and C-peptide were not measured again after the procedure. The patient was discharged from the hospital on glibenclamide monotherapy.

A scheduled re-evaluation 6 months later showed a completely resolved muscle hypotonia. Walking was possible without external support, but he was yet to start talking. Diversification of food was completed successfully, with his weight remaining stable at 13 kg, while he gained 8 cm in length to a height of 83 cm. His HbA1c decreased to 6.5% (47.5 mmol/mol), with normal results for the standard biochemistry panel. Glucose values were generally excellent, with the exception of morning fasting glucose, which remained relatively high (approximately 10 mmol/L / 180 mg/dL). The glibenclamide dose remained unchanged at 0.8 mg/kg/day, but was later steadily increased to 1.6 mg/kg/day, as required by glucose evolution. Re-evaluation at age 2.6 years showed the child spoke syllables, but no words, and pediatric consultation estimated his neurological age to be approximately 12–14 months. There were repeated episodes of various ear and respiratory infections successfully resolved without any insulin support, although the mother admitted that high blood glucose levels were encountered during the peak disease time. His weight was still stable at 13 kg, but his height increased to 88 cm. The dose was increased to 2 mg/kg/day, as HbA1c was 8.5% (69.4 mmol/mol), partially explained by previous infection episodes. One month later (age 2.7 years), the patient’s weight increased to 14 kg, but so did the HbA1c level (8.7%; 71.6 mmol/mol). Consequently, the dose was increased to 2.4 mg/kg/day. The most recent available evaluation was in August 2016 (after 2 years on glibenclamide), when his weight was 16 kg, his height was 94 cm, and electroencephalography and brain magnetic resonance imaging (carried out elsewhere, 7 months previously) were normal, whereas HbA1c dropped to 6.0% (42 mmol/mol). The dose requirement to achieve this level of metabolic control was

![Figure 1](image.png)
CASE REPORT

Ioacara et al.

2.6 mg/kg/day, with a significant improvement in self-monitored glucose values and patient involvement in general activities (still no words spoken). Administration of glibenclamide was carried out every 3–6 h, and the 24-h dose was reported above. Throughout the follow-up period (glibenclamide monotherapy), glucose values were generally on target, with the exception of the midnight to morning period, with morning high blood glucose values. No seizures were reported at all. More frequent dosing was based solely on the clinical finding that a higher dose given less frequently (i.e., every 8 h) seemed to be less effective compared with four smaller doses (early morning, noon, dinner and at bedtime).

DISCUSSION

The present report shows the clinical outcome of the first successful transition to sulphonylurea monotherapy in a patient diagnosed with neonatal diabetes as a result of a de novo p.Q52R mutation in the KCNJ11 gene (c.155A>G). Each of this patient’s offspring has a 50% chance of inheriting this severe mutation, as genetic transmission is autosomal dominant. The low normal birthweight was considered to be the direct result of low insulin concentrations during fetal life. After the diabetes onset, insulin treatment combined with muscle hypotonia was then responsible for overweight presentation at sulphonylurea switch in July 2014. The same ATP-sensitive potassium channels not functioning in the pancreatic β-cells have the same fate elsewhere, including the brain. This explains the severe neurodevelopmental delay before sulphonylurea monotherapy was started. After continuous glibenclamide exposure, there was a rapid improvement in motor skills, especially for muscle hypotonia, but not for the spoken language. Muscle hypotonia seems to be the result of a central neurological dysfunction and not a defect located at the muscular level. Many neurological deficits last through adulthood, but the current clinical presentation of a happy child, full of energy and eager to play, gives hope for the future evolution.

Studies suggested that different mutations in the Kir 6.2 subunit of the potassium channel might have different phenotypes depending on the relative distance from the ATP-sensitive section of the channel. Mutations near the ATP binding site directly inhibit the capacity of ATP to close the channel and are generally associated with milder forms of neonatal diabetes, whereas those located more distally affect the structure of the pore, not allowing for an easy closing, leading to more severe forms of the disease. Unfortunately, the p.Q52R mutation falls in the second category, leading to increased channel ‘rigidity’. The insulin secretion under glibenclamide treatment in the present patient initially lasted a very short time. In our opinion, for this type of mutation there is a strong need for very rapid dose escalation and perhaps multiple dose administrations in a day, as the present case suggests a possible response to glibenclamide well above the 1 mg/kg bodyweight dose range. Blood glucose values significantly improved after 1 week of glibenclamide monotherapy, suggesting improved endogenous insulin secretion. This suggests that some important factors required for insulin secretion machinery are initially missing as a result of long-term inactivity of the β-cells, and time is required for their acquisition, perhaps by new transcriptions being started. At this point, another important aspect of physiopathology needs to be discussed. Based on work carried out by Pearson et al., a very interesting hypothesis arose: for insulin secretion to take place, the coexistence of three factors might be required. First, glucose is taken up and metabolized by the β-cell to generate sufficient ATP near the cell membrane. Second, a sulphonylurea should be present on the SUR1 subunit surrounding the potassium channel in a sufficient concentration to put the channel in a near close state. Third, nutrients must enter the digestive system to enable sufficient glucagon-like peptide-1 to be secreted and finally act on the β-cell. In support of this hypothesis, the present case showed an interesting clinical evolution following casual hyperglycemia. When finding a rising glucose value (i.e., 15 mmol/L/270 mg/dL), one is faced with the dilemma of choosing between two possible options: (i) to administer a new dose of glibenclamide and wait for the glucose to drop; and (ii) give the patient a normal meal, without any glibenclamide. Our clinical experience points in the direction of the somewhat counterintuitive second option, which actually led to a sustained drop in glucose values. The first option was also clinically tested, and led to further rising of the blood glucose levels. The explanation might be in the aforementioned hypothesis, where food might be responsible for the endogenous glucagon-like peptide-1 rise (the missing link to insulin secretion), with glibenclamide half-time long enough to very likely still be available to β-cells, and glucose of course already at high levels. In contrast, as insulin secretion seems to be food-derived glucose-dependent, the risk for hypoglycemia in this very severe mutation is very low, if at all. It seems that ATP concentration near the channels effectively falls when extra- and intracellular glucose concentration drops, so that insulin secretion can be promptly terminated.

As opposed to the patient presented by Shaw and Majzoub, harboring the same Q52R mutation, our case did not experience severe liver dysfunction. The suspected K/ATP channel malfunctioning in the liver as a result of this mutation might have been expressed only in the case presented by Shaw and Majzoub because that baby was born prematurely with perhaps a lower ability to accommodate for this possible liver injury. The phenotype heterogeneity associated with the same mutation is further emphasized by the case presented by Doneray et al. Here, a novel missense mutation (p.Q52L) was found at the same deoxyribonucleic acid location (c.155A>T), in an individual with permanent neonatal diabetes that was not accompanied by any neurological finding, and easily responding to sulphonylurea treatment. The most plausible explanation is that a single switched aminoacid is
responsible for a significant change in the three-dimensional conformation of the channel pore, explaining the phenotype differences between our cases. In the recent article by Babiker et al., the Q52R mutation is placed in the very low sulphonylurea responsive group, listed with only one case of successful switch, which is the above presented case (also part of the Exeter FIND database). As this successful case of being taken off insulin in a carrier of a KCNJ11 Q52R mutation has already been reported in the published manuscript by Babiker et al., this is simply a case report, which provides more clinical details of the management of this case, which would hopefully be of benefit to clinicians managing similar cases in the future.

In conclusion, any patient with diabetes onset before age 6 months should be genetically tested, and then submitted to a center with experience in neonatal diabetes management. When faced with a dreadful genetic finding from the laboratory, the physician must never lose hope, as there is clear indication that no matter how low the a priori likelihoods are, each patient has a significant chance of a better treatment. The Q52R mutation seems to have a chance of positive response to glibenclamide administered every 3–6 h instead of the classical 8–12 h, in doses around or above 2.5 mg/kg/day.

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DISCLOSURE
The authors declare no conflict of interest.

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