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KCNJ11 Gene mutation as a cause of neonatal diabetes and adult-onset diabetes

Phoebe Wamalwa[1]*; Prisca Amolo[2]

[1]Fellow paediatric endocrinology, Department of Paediatrics, University of Nairobi, Nairobi, Kenya.

[2]Paediatric endocrinologist, Department of Paediatrics, Kenyatta National Hospital, Nairobi, Kenya.

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***Corresponding Author:** Phoebe Wamalwa, Fellow paediatric endocrinology, Department of Paediatrics, University of Nairobi, Nairobi, Kenya.
Email: phoebe-j80@students.uonbi.ac.ke

Abstract

Neonatal diabetes is a rare metabolic disorder defined as hyperglycemia occurring within the first 6 months of life with subsequent insulin requirements. It has an incidence rate of 1 in 90,000 to 1 in 160,000 live births. We describe a case of an 8-week-old male infant presenting with persistent hyperglycemia with features of meningitis who was found to have a heterozygous KCNJ11 gene mutation that encodes for Kir6.2 subunit of the ATP sensitive inward potassium rectifying channel, KATP. The genetic results necessitated a successful switch from insulin to a sulfonylurea.

Introduction

Neonatal diabetes is defined as persistent hyperglycemia occurring within the first 6 months and occasionally between 6 to 12 months of life [1]. The cause is most of the times a genetic defect hence the need to conduct genetic analysis in all infants presenting within the first 6 months of life [1]. Several genes have been studied as the cause of this condition and they can be classified into those that regulate pancreatic development like PDX1, HNF4A, HNFA1, FOX1, NEUROD1; those that are related to abnormal beta-cell function like INS, GCK, SLC19A2, GLUT2, KCNJ11, ABCC8 and those that are associated with beta cell destruction like WRS1, IER3IP1 and EIF2AK3 [2]. KCNJ11 and ABCC8 gene defects are the most common cause of permanent neonatal diabetes [3]. KCNJ11 together with ABCC8, a gene that encodes the SUR1 subunit, regulate the ATP sensitive potassium channel which regulate insulin release in conjunction with the calcium channel [1]. We report a case of an 8-week-old infant who was diagnosed with a heterozygous KCNJ11 gene mutation and has successfully been transitioned to sulfonylurea.

Case description

The patient, D. M, was brought to the national referral hospital at 8 weeks of age as a referral from one of the county hospitals with a two-day history of difficulty in breathing, fever and convulsions. There was no history of cough, diarrhea or yellowness of body. The convulsions were reported as tonic-clonic lasting approximately three minutes. Fever had been recorded as high as 39° C and did not respond to paracetamol.

The child was born to a non-consanguineous couple via spontaneous vertex delivery at 39 weeks gestation. He cried immediately after birth and weighed 3.1 kg. There was no reported neonatal hypoglycemia or hyperglycemia. He was on exclusive breastfeeding and no feeding intolerance was noted. There was no developmental delay. His previous medical history was non-remarkable. His paternal grandfather had diabetes and was on insulin with poorly controlled sugars. He was the second born child. His elder sibling was a 4-year-old male with no known medical condition. On examination he had no dysmorphism and was found to be moderately pale, mildly dehydrated and had a pulse rate of 140 beats per minute. The respiratory rate was 43 breaths per minute and his oxygen saturation on pulse oximetry was 90% on room air. He had normal muscle tone and bulk, and a head circumference of 41 cm. There were no skeletal abnormalities, macroglossia or umbilical hernia. The cardiac system was normal clinically. The rest of the systems were unremarkable.

A random blood sugar revealed a hyperglycemia of 22.3 mmol/L. The blood gas analysis showed a pH of 7.4 (7.35-7.45), PCO2 2.4 kPa (5.1-5.6), PO2 10.1 kPa (10.5-13.5), lactate of 2.6 mmol/L (<2.0) and bicarbonate of 15.1mEq/L (22-28). Urinalysis done showed moderate glucosuria with mild ketones. Blood sample was sent for full hemogram that showed mild normochromic anemia. Cerebrospinal fluid biochemistry revealed very high protein with low glucose and although the culture was negative, a diagnosis of meningitis was entertained. Kidney and liver function tests were normal.

He was put on management with 0.9% saline and potassium chloride supplementation, insulin infusion at an initial dose of

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0.03U/kg/hour which was later increased to 0.05U/kg/hour. Treatment for infection was also started with ceftazidime but this was later changed to meropenem due to poor clinical response. On subsequent days, the high sugars persisted in the range of 8 to 14 mmol/L despite insulin and antibiotics and therefore additional tests were requested. These included glycated hemoglobin (HbA1C) which was 5.1%, pancreatic ultrasound which was normal, glutamic acid decarboxylase 65 (GAD 65) autoantibodies and tyrosine phosphatase-like insulinoma antigen 2 (1A2) antibodies which were negative. The non-fasting C-peptide was 0.26 ng/ml (0.5-2.7). Pancreatic amylase levels were <5U/L (0-90) while the pancreatic lipase was 14 U/L (0-70).

D. M improved slowly and breast feeding resumed gradually. Convulsions and fever subsided and he was hence transitioned to glargine insulin at 0.5U/kg/day in two divided doses. During treatment, he developed pus discharge at the site of intraosseous placement hence clindamycin was added to the treatment. In the course of his stay in the hospital, diabetes education was given to the mother in terms of correction of hypoglycemia with rapid acting carbohydrates and hyperglycemia with aspart insulin. However, the sugars remained high and the dose of glargine insulin was increased to 0.8 U/kg/day. A discussion on genetic testing was initiated, and he was allowed home to be followed up in the paediatric endocrine clinic.

A month after diagnosis, samples for genetic testing were taken from the patient and both parents and sent to University of Exeter medical school genetic laboratory in United Kingdom for analysis. The test methodology involved analysis of coding and flanking intronic regions of the ABCC8, KNJ11 and INS genes (NM_001287174.1, NM_000525.3 and NM_001185098.1) by Sanger sequencing. The report confirmed that our patient had a pathogenic heterozygous KCNJ11 missense variant (NM_000525.3: c.149G>Ap. (Arg50Gln); location: GRCh37(hg19): Chr11: g.17409490C>T.

The mother to the patient was not found to have the pathogenic KCNJ11 variant. However, the father was found to have the subtype KCNJ11 with similar variant details like his son, hence genetically predisposed to diabetes. On further inquiry, the father reported a recent random blood sugar reading of 8.3 mmol/L but the HbA1C done later was 5.7% (4.0-7.5%). He however did not report symptoms of diabetes nor any neurodevelopmental features. The patient's paternal grandfather is a known patient with diabetes on insulin and sulfonylurea.

The general progress of the baby while on insulin was fair with blood glucose levels ranging from 5 to 11 mmol/L in the first 2 months post discharge. There was a reported accelerated weight gain with a weight of 7.8kg being attained at 4 months of age. No seizures have been reported after discharge. He was switched to sulfonylurea at 0.05mg/kg in 2 divided doses initially after the genetic results came back. This dose was subsequently titrated down to 0.025mg/kg/day with close monitoring after several reports of hypoglycemic episodes. The blood glucose has since been ranging from 4.2 mmol/L to 7.5 mmol/L. However, there are a few reported high blood sugar levels during respiratory tract illnesses. The child has remained active; he hears well and can walk with support at 11 months of age. The speech development is normal per age. The head circumference at 11 months was 45.5 cm.

Discussion

Among patients diagnosed with diabetes mellitus before 6 months of age, about 80% have been found to have a genetic etiology [4]. A monogenic cause of neonatal diabetes should be considered in all infants who present before 6 months of age regardless of the presence of autoimmunity, and in those presenting between 6 and 12 months of age with absent autoimmunity, an unusual family history or other congenital defects [5].

KCNJ11 mutation is one of the most common causes of permanent neonatal diabetes with 90% occurring due to a spontaneous mutation [6] and the familial cases being inherited in an autosomal dominant fashion [5]. This is an activating mutation that prevents closure of the KATP channel thus reducing secretion of insulin [7]. Here we report the first case of neonatal diabetes with a genetic diagnosis from our center. Our patient and his father were found to have a KCNJ11 variant implying that this was an autosomal dominant inheritance. His paternal grandfather who had diabetes, although not tested, most likely may have the same variant. The recurrence risk in our patient's siblings is thus 50%.

Our patient did not have intrauterine growth restriction which occurs due to deficiency of insulin which is required for growth [8]. He has also had normal neurodevelopment to date. KCNJ11 mutation is associated with neurodevelopmental impairment due to the expression of KATP channels within the brain [9]. This may range from mild cognitive impairment to severe cases presenting with epilepsy [10].

Up to 90% of patients with KCNJ11 mutations can be successfully switched from insulin to sulfonylureas with improved glycaemic control [2]. Sulfonylureas bind to the SUR1 subunit of the KATP channel thus inducing closure of the channel and increasing insulin secretion [11]. There is some evidence that sulfonylurea therapy improves neurologic symptoms, but this benefit depends on how early treatment is initiated [12-14].

Identification of a genetic cause of neonatal diabetes is important as it improves clinical care as is demonstrated in our case. We were able to switch to sulfonylurea therapy, which is more effective, easier to administer and less costly than insulin therapy. In addition, the genetic testing enabled us to classify the diabetes and provide genetic counseling to the family. It also triggered screening for diabetes in the father who had the same mutation but was asymptomatic. This case not only highlights the importance of genetic testing, but also the challenges encountered in resource limited settings. There are no local molecular genetic laboratories, hence samples

must be taken out of the country. The Exeter university laboratory conducted the tests for free, but the cost of handling and transport of the specimen was borne by the patient. Since neonatal diabetes has multifactorial causes besides genetics one can quickly rule out congenital anatomical causes like pancreatic agenesis through an ultrasound and pancreatic disease through exocrine pancreatic function tests like amylase and lipase. Whereas most genetic defects may respond to sulfonylureas, a few others still require insulin. There is no clear-cut differentiating clinical presentation to inform whom to treat with insulin or sulfonylurea. However, giving a trial of sulfonylureas in the absence of genetics may be used in resource limited areas but with a high risk of abuse by clinicians. In conclusion this case validates the recommendation to test all neonates presenting with persistent hyperglycemia to confirm specific genetic defects. It also corroborates various reports that have shown successful switch from insulin to sulfonylureas in management of neonatal diabetes. Genetic testing for monogenic diabetes needs to be availed locally for accurate management.

Ethical disclosures: The Kenyatta National Hospital-University of Nairobi (KNH-UoN) Ethics Committee granted written approval for this case to be reported. The authors obtained written informed consent from the guardian of the patient mentioned in this article.

Conflicts of interest: The authors have no conflict of interest to declare.

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