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CASE REPORT

Transient neonatal diabetes due to a missense mutation (E227K) in the gene encoding the ATP-sensitive potassium channel (KCNJ11)

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Key Clinical Message

Neonatal diabetes is a monogenic form of diabetes. Herein, we report on a newborn presenting diabetic ketoacidosis at 17 days of life . A KCNJ11 mutation was identified. In such cases, insulin can be replaced by sulfonylurea with a successful metabolic control, as an example of how molecular diagnosis may influence the clinical management of the disorder.

Keywords

Insulin, K_{ATP} sensitive channels, *KCNJ11* gene, neonatal diabetes mellitus, sulfonylureas.

Introduction

Neonatal diabetes mellitus (NDM) is a rare monogenic form of diabetes starting within the first 6 months of life [1–3]. The disease has an incidence of about 1:100,000–260,000 live births and can be permanent (PNDM), requiring lifelong treatment, or may be transient (TNDM), in which case the diabetes may spontaneously remit (or be so mild as not to require treatment), but will often relapse, usually during adolescence [3–5].

TNDM comprises approximately 50% of children with neonatal diabetes [6]. A genetic diagnosis has been made in up to 90% of these patients [7]. In the majority of them (around 70%), it was found that a genetic or epigenetic alteration in the TNDM locus on chromosome 6q24 causing the overexpression of two imprinted genes [7]. Less frequently, activating mutations of the genes *KCNJ11* and *ABCC* (accounting for 10% and 13% of the cases, respectively) may result in TNDM [7]. Mutations in these genes lead to a gain-in-function of the pancreatic ATP-sensitive potassium (K_{ATP}) channel, which is critical in the regulation of insulin secretion by the beta cell [3, 6, 8, 9].

The beta cell K_{ATP} channel is an octameric complex composed of four pore-forming subunits: channel-building inwardly rectifying potassium-channel subunits (Kir6.2) encoded by the *KCNJ11* gene, and four regulatory sulfonylurea-receptor subunits (SUR1) and encoded by the *ABCC8* gene [10, 11]. These subunits regulate the metabolic activity of the channel, which is shut down in response to an increase in intracellular ATP, leading to insulin secretion. Gain-in-function mutations of either of these genes keep the channel in open conformation and impair insulin secretion [10–12].

Most patients with *KCNJ11* mutations treated with insulin can be transferred to sulfonylurea (SU) with a remarkable improvement in metabolic control and patient's quality of life [13]. Sulfonylureas close K_{ATP} channels, through an ATP- independent route, improving insulin secretion and representing a suitable therapeutic alternative for patients with *KCNJ11* mutations [10]. For these rea-

sons, identification of K_{ATP} channel mutation can have a major impact on the treatment's choice. This is an example about how molecular diagnosis can influence the clinical management of the patients.

Herein, we report on a case of NDM in a Caucasian boy, who presented severe diabetic ketoacidosis (DKA) at 17 days of life. The disease remitted 4 months later. The genetic screening showed a heterozygous missense mutation (c.679 G>A) in the *KCNJ11* gene which leads to the replacement of lysine with glutamic acid at position 227 (E227K) of the ATP sensitive potassium channel.

Case Report

An 11-day-old Caucasian boy was admitted to the neonatal care unit with complaints of poor weight progression, suppurative conjunctivitis, and mucoral candidiasis. He was the second child of a 21-year-old woman (gravida 2, para 1) without history of diabetes, and was born through cesarean section at 38 weeks of pregnancy due to preeclampsia. APGAR score was 5/9/10; birth weight was 2890 g (p15), length 47 cm (p15) and head circumference 34.5 cm (p50) [14]. On physical examination, the infant exhibited axial hypotonia and weak suction reflex, demanding a nasogastric tube in order to be feed. At 17 days old, a sudden deterioration of his general condition was noticed. The child became irritable, drowsy, dehydrated, tachypneic, tachycardic with poor peripheral perfusion; rectal temperature was 37.8°C. He was started on intravenous vancomycin after isolation of a methicillin-resistant staphylococcus from the axillary suppurative adenitis. Blood tests revealed a glycemia of 1412 mg/dL with high levels of ketonemia; serum sodium was 172 mmol/L; potassium 3.9 mmol/L, and the pH was 7.0. After initial treatment with intravenous 0.9% saline serum, he was started on intravenous insulin perfusion (0.01 U/kg/h) in a 0.45% saline serum supplemented with 15 mEq/L of potassium chloride. Blood glucose was brought to normal levels and the acidosis was corrected. Three days later, the insulin perfusion was stopped and the child was transferred to a subcutaneous protocol of intensive insulin therapy, consisting in a once daily administration of insulin glargine (1 U/day), and insulin lyspro every 6 h. Further investigations revealed that there was no evidence of pancreatic exocrine failure. Transfontanelar and abdominal ultrasounds; electroencephalography and brain magnetic resonance imaging showed no relevant findings. An interatrial communication "*ostium secundum*", associated with enlargement of right cavities was found in the echocardiogram. C-peptide was 0.37 ng/mL (0.80–4.20); auto antibodies against islet cell (ICA), decarboxylase of glutamic acid (GAD), and insulin were all negative. Thyroid function test was normal.

At the age of 2 month, the infant was referred to a tertiary hospital due to instability of his metabolic control, alternating episodes of hypoglycemia with hyperglycemia. He was put on an insulin pump device with continuous glucose monitoring. There was a progressive normalization of his glycemia and the insulin needs declined gradually. Two months later, insulin administration was stopped, given that glycemia was always within normal levels with minimal amounts of insulin. At this stage, the C-peptide was already normal. At the age of 9 months, his growth had declined from p10 to $p<1$. Simultaneously, his body weight decreased from p15 to $p<1$. He was extubated by this time, but his neurodevelopment is still abnormal.

Discussion

The E227K mutation found in our patient is a gain-function mutation that results in both impaired ATP sensitivity and higher intrinsic 'open probability' of the K_{ATP} channel, causing impairment in insulin secretion [11]. The E227K mutation has been reported in several other patients with TNDM but also in a few with PNDM reflecting the phenotypic variability of *KCNJ11* mutations (Table 1). The reason why the same mutation causes a relapsing/remitting form of diabetes in some patients whereas in others it produces a permanent diabetes is unclear [15]. It was not demonstrated a clear relationship between the clinical phenotype and the magnitude of the impairment of the ATP-sensitive potassium (KATP) channels. TNDM may result from a reduction in insulin requirements at the time of remission due to changes in beta cell turnover or to compensatory alterations (at the level of the beta cell, pancreas, or whole body), overcoming the lower effectiveness of the ATP sensitive potassium channel. Therefore, the genetic background of the patient as well as other still unrecognized environmental factors may play an important role in the phenotypic expression of the mutation. On the other hand, the apparent clinical variability may result from confounding factors: patients diagnosed during puberty or early adulthood may have had a period of hyperglycemia that was missed during the neonatal period.

The E227K may be inherited from affected parents, or occurs as *de novo* mutation. In our study, the mutation is present in the affected child but also in his asymptomatic mother, suggesting that there was not a complete co-segregation of the mutation with diabetes. This situation has also been described previously (Table 1).

In the majority of TNDM and PNDM cases caused by *KCNJ11* mutations [3, 13], including E227K mutations [11], metabolic control was achieved by replacing insulin therapy with sulfonylureas, which are well-known K_{ATP} channel inhibitors (Table 1). This finding supports the

Table 1. Clinical data of patients with heterozygous E227K mutation.

E227K Mutation *KCNJ11* gene	Age at onset	Clinical presentation	Evolution	Initial treatment	Transition to sulfonylurea
Edghill, et al. [19]					
Family – ISPAD 57: German Maternal allele					
Patient 1 (Index case, male)	?	?	Transient	?	?
Patient 2 (Maternal half sister)	?	?	Transient	?	?
Patient 3 (Maternal half sister)	?	?	? (Carrier?)	?	?
Patient 4 (Mother, *de novo* mutation)	?	?	Transient	?	?
Family- ISPAD 114: Canada Paternal allele					
Patient 1 (Index case, male)	?	?	Transient	?	?
Patient 2 (Father, *de novo* mutation)	?	?	Transient	?	?
Flanagan, et al. [6], UK					
Family 1					
Patient 1 (Index case, male)	6 wks	?	Transient Remission 31 wks	Insulin	No
Patient 2 (Maternal half sister)	8 wks	?	Permanent	Insulin	No
Patient 3 (Maternal half sister)	—	—	Asymptomatic carrier	—	—
Patient 4 (Mother)	Birth	?	Transient Remission 36 wks Relapse 25.5 yrs	Insulin	No
Family 2					
Patient 1 (Index case, male)	13 wks	?	Transient Remission 52 wks Relapse 6 yrs	SU	
Patient 2 (Father)	23 yrs	?	Diabetic (neonatal? permanent/transient?)	SU	
Rica, et al. [20], Spain					
Patient 1 (Index case, female)	93 days	Hyperglycemia	Transient Remission ~195 days	Insulin	No
Patient 2 (Father)	?	?	Diabetic (neonatal? permanent/transient?)	?	No
Støy, et al. [21], USA					
Patient 1 (Index case, female)	5 wks	DKA	Transient?	Insulin	
Patient 2 (Father)	?	?	MODY-like phenotype	Insulin	
Extensive diabetes family history of autosomal dominant transmission, but none of them with NDM. All were diagnosed in their twenties and were nonobese, with some on insulin therapy and others on oral antidiabetic agents.					
Kochar, et al. [22], India					
Patient 1, male (*De novo* mutation)	4 mth	DKA	Transient Remission- 6 mth	Insulin	Successful
Abbasi, et al. [11], Iran					
Patient 1 (Sibling, male)	40 days	Poor weigh gain, hyperglycemia	Permanent	Insulin	Successful
Patient 2 (Sibling, male)	2 yrs	DKA	Diabetic	Insulin	Successful
Patient 3 (Father)	15 yrs	Polyurea Polydipsia Developed proliferative retinopathy	Permanent	Insulin	Successful
Vakili, et al. [23], Iran					
Patient 1 (female)	2 mth	DKA	Transient Remission 9 mth	Insulin	Not tried
Patient 2 (female)	2 mth	DKA	Transient Remission 7 mth	Insulin	Successful
Azores, 2013					
Patient 1 (Index case, male)	17 days	DKA	Transient Remission- 4 mth	Insulin	Not tried
Patient 2 (Mother)	?	?	Asymptomatic carrier	?	?

Wks, weeks; mth, months; yrs, years; DKA, diabetic ketoacidosis; MODY, maturity-onset diabetes of the young.

idea that if our patient has a relapse of diabetes, he may achieve optimal glycemic control with oral sulfonylurea treatment, strengthening the importance of the molecular diagnosis even if neonatal diabetes remits.

The expression of *KCNJ11* in the central nervous system and skeletal muscle explain the neurological features associated with syndromic forms of PNDM, such as developmental delay, muscle weakness, and epilepsy [16, 17]. However, neurological features were also identified in patients with nonsyndromic forms of PNDM and TNDM who carried *KCNJ11* mutations as speech delay, autistic spectrum disorder, and learning disability. Until now it is

difficult to assure whether these complications are a consequence of the mutation or whether environmental and/or other genetic factors are involved [6]. In the case herein reported, the infant exhibited axial hypotonia and weak suction reflex, that may be caused by the mutation or/and may be due to exposure to hyperglycemia and ketosis during the first days of the child's life [1, 3, 18]. Further studies are necessary to clarify the etiology of neurological impairment in TNDM patients who carried KCNJ11 mutations and to access the effectiveness of SU in improving the neurological development.

In conclusion, *KCNJ11* activating mutations may be an important cause of TNDM. Molecular diagnosis should be performed in order to identify those patients who may benefit from SU therapy. Further investigation is required to understand clinical heterogeneity and the incomplete co-segregation of the *KCNJ11* mutation with diabetes, and also the molecular mechanisms underlying the biphasic course of TNDM.

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Conflict of Interest

None declared.

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