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Case Report

Permanent Neonatal Diabetes Mellitus Associated with a New EIF2AK3 Mutation: A Case Report

Nasthia Coraly Quilismal[1*], Nadia Catalina Arguiñarena[1], María Rosa Finozi[1].

1. Servicio de Endocrinología Pediátrica. Hospital Pereira Rossell. Montevideo (Uruguay).

[*]**Correspondence to:** Nasthia Coraly Quilismal, Pediatric Endocrinology Service Pereira Rossell Hospital. Montevideo Uruguay, Pocitos, Av Echevarriarza 3299.

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Abstract

Neonatal Diabetes Mellitus (NDM) is a subtype of monogenic diabetes. Clinical manifestations, treatment, and prognosis will depend on the affected gene; identifying the etiology allows choosing the treatment, assessing other repercussions, and implementing a follow-up plan. We present the case of an infant aged 1 year and 6 months, with no personal or family history. Presents at 3 months of age polyuria, polydipsia, asthenia, fever, and vomiting, paraclinical glycemia 574 mg/dL, ketonemia +++, pH 7.28, HCO3 14.1. Diagnosed with mild diabetic ketoacidosis (DKA), he received hydration with physiological serum and Crystalline insulin. At 48 hours, the DKA was resolved, NPH insulin was started, and adjustments with Crystalline insulin, granting discharge with a corrective bolus basal plan. The genetic study revealed the variant of uncertain significance c.2969A>G p. (Tyr990Cys) homozygous in the EIF2AK3 gene. At present, he maintains good metabolic control and weight and height development.

***Keywords**: Diabetes Mellitus, Insulin, congenital, mutation.*

Introduction

Neonatal Diabetes Mellitus (NDM) is a subtype of monogenic diabetes detected in the first 6 months of life, without the presence of antipancreatic autoimmunity and requiring insulin therapy for at least two weeks. It occurs in almost 1 in 100,000 newborns (1) and represents 2.5% to 6.5% of monogenic DM of childhood (2). It is caused by mutations in one of the genes involved in the synthesis, release, or action of insulin (1). Fifty to sixty percent of cases are derived from mutations in one of the genes that regulate the normal functioning of the ATP-sensitive potassium (K) channel of the beta cell of the pancreas; other mutations occur due to alterations in the insulin gene (INS) or abnormalities of the 6q24 locus (1). In 75-80% of cases, the genetic alteration can be identified (3). Another subtype of anomalies causing NDM is related to syndromes (4). Such as Wolcott Rallison syndrome, caused by recessive mutations of the EIF2AK3 gene (2p11.2), in which consanguinity exists in the majority of cases (5). The clinical manifestations of NDM are widely variable depending on the etiology (6). Extra-pancreatic findings may be useful in identifying the underlying genetic mutation (2). Two forms of NDM are distinguished based on the time of treatment, transient NDM (TNDM),

and permanent NDM (PNDM) (4). For patients with persistent hyperglycemia, initial treatment is aimed at correcting fluid and electrolyte abnormalities and reducing hyperglycemia by administering insulin (6). Insulin therapy is crucial in PNDM to achieve adequate weight gain and growth (7). Insulin therapy is complex due to the infant's diet compromising calorie intake, lack of a pharmacokinetic profile for subcutaneous insulin administration at this age, the need for very small doses prone to errors in administration (7), and the narrow margins between hyperglycemia and hypoglycemia, both dangerous for the neurological development of the newborn (8). The following is a case report of a patient with NDM with a mutation in the variant c.2969A>G p.(Tyr990Cys) homozygous in the EIF2AK3 gene. Considering the limited data on this pathology, it is essential for the medical community to have new information on the subject.

Clinical Case

Male infant aged 1 year and 6 months, with a perinatal history of 36 weeks preterm, appropriate for gestational age, Apgar 7/9, and normal neonatal screening. No personal or family history of note, no consanguinity between parents. Presented at 3 months of age with diabetic debut in the form of mild diabetic ketoacidosis (DKA) (table 1) requiring admission to the intensive care unit (ICU). HbA1c 11%, C-peptide 0.18 (normal range 0.10-2.55), normal thyroid profile, abdominal ultrasound showing pancreas and liver with usual characteristics. Received treatment with 20 ml/kg physiological saline and regular insulin 0.01 IU/kg/hour intravenously (IV). Due to good progress, a switch to subcutaneous NPH insulin 0.2 IU/kg/day was made at 48 hours, with adjustments with lispro insulin of 0.5 IU from 200 mg/dl of blood glucose in self-monitoring every 3 hours. Given the tendency to hyperglycemia, prandial boluses with lispro insulin were initiated.

Discharge was granted within a month with clinical improvement and a basal-bolus-corrective plan. Diagnosis of the variant of uncertain significance c.2969A>G p.(Tyr990Cys), homozygous, in the EIF2AK3 gene was made through a panel of genes associated with NDM. Currently under monthly follow-up by a multidisciplinary team consisting of endocrinology, diabetes educator, nutritionist, pediatrician, and geneticist. Good weight and height growth and good development are observed, without skeletal dysplasia or hepatic dysfunction in the current follow-up. Presents poor metabolic control, with glycated hemoglobin (A1c) of 8%. Due to poor metabolic control and age, a switch from NPH insulin to Degludec was made, with a marked improvement in glycemic control.

Table 1. Analytical Results at Diagnosis

Parameter	Result	DKA values
Glucose	574mg/dl	Glucose >250 mg/dl
Ketones	+++	+
pH	7.28	7.3
Bicarbonate	14.1	<18

Discussion

NDM occurs due to mutations in genes regulating pancreatic beta cell function, damage to the same, or pancreatic hypoplasia/aplasia. More than 20 responsible genes have been found, and in most cases, mutations occur in genes encoding the ATP-sensitive potassium (K) channel of the pancreatic beta cell (1). For etiological diagnosis, the use of genetic tests is recommended, unless there is highly suggestive clinical evidence of the underlying mutation (2), such as in the case of NDM related to syndromes, such as Wolcott Rallison syndrome, a rare autosomal recessive disease caused by mutations in the EIF2AK3 gene (2p11.2)(1). However, NDM presents wide clinical variability, making genetic tests an almost indispensable tool for etiological diagnosis, guiding appropriate insulin or sulfonylurea treatment (9), and predicting the potential for related complications or diseases. Therefore, tests should not be delayed and should be performed before the first year of life, in patients diagnosed with DM, especially if they have negative antibodies, although the presence of autoantibodies does not rule out a monogenic cause of DM (10). In our patient, a mutation in the EIF2AK3 gene was found; mutations in this gene correlate with Wolcott Rallison Syndrome, characterized by NDM, skeletal dysplasia, and hepatic dysfunction, usually presenting during the first year of life and is the main cause of NDM associated with paternal consanguinity (3). However, our patient presents a new variant of mutation in the mentioned gene, currently only presenting NDM during follow-up. The diagnosis of NDM should be suspected in the presence of sustained hyperglycemia for at least two weeks in newborns or infants under 6 months of age, in the absence of other known causes of hyperglycemia (11).

Clinical manifestations vary widely, ranging from asymptomatic hyperglycemia, small for gestational age (SGA), inadequate postnatal growth, polyuria, glucosuria(12), and in severe cases, patients may experience weight loss at onset due to vascular volume depletion, ketonemia, acidosis, dehydration, and electrolyte abnormalities due to polyuria, as seen in our patient who presented with DKA at 3 months of age.

Insulin therapy is key as it promotes growth through its indirect effect on somatomedin C secretion and directly improves nutrition (13). NDM may require treatment until approximately 18 months of age, being transient in 30% of cases, especially in 6q24 mutations and mutations in the KCNJ11 and ABCC8 genes, while PNDM requires lifelong treatment (10). Given our patient's age of 18 months with ongoing insulin requirements and a novel EIF2AK3 mutation, it is considered a case of PNDM.

Treatment focuses on carbohydrate intake balance (15-18 g/kg/day of carbohydrates), necessary to restore normal weight and prevent future insulin resistance, and sufficient insulin treatment to achieve metabolic balance (13). Insulin therapy in PNDM allows satisfactory weight gain and growth in these children. The initial insulin dose ranges from 0.01 to 0.05 units/kg/hour depending on severity, with adjustments in small increments of 0.01 units/kg/hour to slowly decrease blood glucose and maintain values between 100-200 mg/dl. However, dosing should ultimately be guided by clinical judgment, with hourly monitoring during intravenous infusion and then every 8 hours (14).

Continuous subcutaneous insulin infusion (CSII) pumps are preferred as they reliably deliver small doses due to their physiology, safety, and ease of use (14). CSII most commonly uses rapid-acting insulins or ultra-rapid analogs (Aspart, Lispro, Glulisine), considered the first choice as they provide greater reduction in HbA1c than regular insulin. However, Aspart is approved for use in children over 2 years old and Glulisine in those over 6 years old, leaving Lispro as the option approved for use at any age, along with regular insulin (15).

In cases where CSII is unavailable, rapid-acting insulins can be administered intravenously until acceptable glucose levels of 100-200 mg/dl are reached, then switched to subcutaneous administration schemes, basal-plus or basal-bolus-corrective, according to patient requirements, combining rapid and intermediate, slow, and ultra-slow acting insulins (16). In our patient, management began with intravenous regular insulin at a dose of 0.01 IU/kg/hour.

With a positive response, a transition to subcutaneous insulin was achieved later, in a basal-bolus-corrective regimen with NPH and Lispro insulin. During the course of treatment, due to repeated hyperglycemia episodes, NPH insulin was switched to Degludec insulin, resulting in improved metabolic control.

Long-acting insulin analogs (Detemir, Glargine) and ultra-long-acting insulin analogs (Degludec) have demonstrated advantages over intermediate-acting insulin in several studies. Their pharmacodynamic profile is flatter and more stable, providing more effective glycemic control while maintaining a lower risk of hypoglycemia (15).

Degludec insulin is an ultra-long-acting insulin and can be used in children with Diabetes Mellitus from the age of one year (16). A study comparing the pharmacokinetics of Degludec in adults and children found that

Degludec's properties are similar in both groups, offering a uniform effect on glycemic control (17).

Another indispensable tool in the treatment of these patients is capillary blood glucose monitoring with glucose meters capable of providing reliable values with the least amount of blood possible (e.g., 0.3 µl of blood). Few devices meet this criterion, and an alternative is the use of continuous glucose monitors either isolated or combined with insulin pumps (4).

After achieving euglycemia with insulin and ruling out pancreatic aplasia/hypoplasia, consanguinity, or syndromic features, an empirical trial of sulfonylureas is suggested in all patients while awaiting the results of genetic tests (6). However, in our patient, given the findings of his new variant, insulin therapy and follow-up with a multidisciplinary team are maintained to ensure good metabolic, growth, and neurological control and to early identify the possible development of other syndromic characteristics associated with the found genetic mutation.

Conclusions

NDM is a rare entity, and its management poses a challenge for the multidisciplinary team responsible for these patients.

In patients with PNDM due to mutations in EIF2AK3, insulin therapy is essential and allows for adequate growth and neurological development.

Patients with PNDM require lifelong follow-up regardless of the genetic mutation they present. Syndromic NDMs associate with extra pancreatic characteristics that may lead to a worse prognosis.

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