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Permanent Neonatal Diabetes with High Insulin Requirements due to a New Variant in the *INS* Gene

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What is already known on this topic?

The three most frequent pathogenic variants that cause permanent neonatal diabetes involve the *ABCC8*, *KCNJ11*, and *INS* genes. The latter is responsible for 10-20% of cases and results in variable clinical behavior, associated with intrauterine growth restriction, maturity onset diabetes of youth-type diabetes, and permanent or transient neonatal diabetes.

What this study adds?

This study reports a novel pathogenic variant within the *INS* gene, not documented in databases. Unlike neonatal diabetes due to *ABCC8* and *KCNJ11* variants, the *INS*-related form does not respond to sulfonylurea treatment and requires insulin for glycemic control, posing a challenge for breastfeeding patients. This report further supports the need for a clinical approach motivated by early molecular diagnosis.

ABSTRACT

Neonatal diabetes is an infrequent disorder that may present as transient, permanent, or syndromic. It is most commonly caused by pathogenic variants involving the *ABCC8*, *KCNJ11*, and *INS* genes. This report describes a neonate with permanent diabetes mellitus due to a previously unreported variant in the *INS* gene, outlining the diagnostic complexities, therapeutic interventions, and related clinical challenges. The neonate with a history of symmetrical intrauterine growth restriction presented with severe hyperglycemia not associated with ketosis or infectious. He had high insulin requirements and did not respond to sulfonylurea management. Anti-insulin and anti-islet pancreatic antibodies were negative. Genetic sequencing revealed a homozygous missense variant (c.3G>A, p.Met11Ile) in *INS*, which had not been previously reported. Timely molecular diagnosis of neonatal diabetes enabled optimization of management strategies, mitigating the long-term impact on growth, neurodevelopment, and the occurrence of hypoglycemic episodes.

Keywords: Neonatal diabetes mellitus, newborn, insulin gene

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Introduction

Neonatal diabetes mellitus (NDM) is a rare genetic condition, with a prevalence ranging from 1/21,000 to 1/300,000 live births, varying by geographical location (1,2). In Europe, the prevalence is estimated to be between 1/90,000 to 1/300,000 live births (3). In regions with high consanguinity, such as the southeastern Anatolia region of Türkiye and the Middle East, the prevalence may increase to between 1/21,000 and 1/48,000 live births (1). The onset of NDM typically occurs within the first six months of life, although cases with later presentation, between 9 to 12 months, have been documented (2,3).

The diagnosis of NDM should be suspected when plasma glucose levels exceed 150-250 mg/dL, particularly after excluding other potential causes of hyperglycemia, including sepsis, low birth weight, or prematurity-associated complications, and medications such as phenytoin, glucocorticoids, ionotropic or high dextrose infusions (4,5,6). Autoimmune diabetes should also be ruled out through negative antibodies testing against glutamic acid decarboxylase, insulin, zinc transporter, and tyrosine phosphatase. A key biochemical feature of NDM is reduced levels of basal insulin and C-peptide (4,5).

To date, over 40 genes have been implicated in the pathogenesis of NDM, with different inheritance patterns. These genes affect insulin synthesis, action, and secretion by altering beta cell development (aplasia and pancreatic hypoplasia), increasing beta cell destruction by apoptosis or protein misfolding with consequent endoplasmic reticulum stress due to retained proteins, and altering beta cell membrane depolarization leading to failure to secrete synthesized insulin into the circulation (3). The three most frequently involved genes are *ABCC8*, *KCNJ11*, and *INS*. The latter is located on chromosome 11p15.5, is responsible for 6.7 to 18% of cases, and results in variable clinical behavior associated with intrauterine growth restriction (IUGR) and maturity onset diabetes of youth-type diabetes (1,7).

This report presents a case of NDM due to a novel pathogenic variant in the *INS* gene, with strikingly high insulin requirements. This report also highlights the role of molecular diagnostics in establishing timely and effective management.

Case Report

A male neonate, aged two days, was admitted to the neonatal unit. The patient's mother, aged 18 years, was experiencing her first pregnancy. The baby was delivered via Cesarean section at 35 weeks of gestation, with a birth weight of 1,310 grams, length of 44 cm, and a head circumference of 29 cm (length-for-age Z score -1.05, weight-for-age Z score -2.71, and head circumference-for-age Z score -2.27 by Intergrowth-21 standards) (8). There was no familial history of consanguinity.

The neonate initially demonstrated adequate adaptation but developed clinical deterioration within the first two days of life, which was characterized by severe anemia necessitating transfusion, intermittent sinus bradycardia with a normal echocardiogram, and persistent hyperglycemia with blood glucose levels reaching 574 mg/dL. After the exclusion of infectious etiologies, familial medical history, and medication-induced hyperglycemia, a diagnosis of NDM was considered. Notably, the early onset severe anemia was not attributable to this condition; occult perinatal blood loss was considered, although not documented, and other causes, including hemolysis and sepsis, were evaluated but not demonstrated.

The patient was initially managed with an intravenous insulin infusion at a rate of 0.07 U/kg/h. Subsequently, insulin Detemir was introduced at a maximum dose of 0.8 U/kg/every 12 hours, in conjunction with insulin Aspart administered in a flexible scheme. Due to the high prevalence of *ABCC8* and *KCNJ11* mutations in NDM, a therapeutic trial with sulfonylurea was conducted, but this yielded no improvement in glycemic control. Following sufficient weight gain, Detemir was replaced with insulin Glargina, and the patient continued with preprandial insulin Aspart, necessitating a progressive dose increase. He was discharged from the neonatal unit at three months of age, requiring 1.7 U/kg/day of insulin and has been followed up every 3-4 months. Insulin requirements have been variable (min. 0.726 U/kg/day-max. 1.26 U/kg/day). Improvement in his World Health Organization standard deviations for height was also documented [from -2.24 standard deviation (SD) at 3 months to -1.41 SD at 50 months].

His neurodevelopment has been normal, but at 2 years and 4 months, he experienced seizures not associated with hypoglycemia. An electroencephalogram detected an occipital focus of discharge, without morphological abnormalities. He has been treated with oxcarbazepine and has been seizure-free since the age of 2.

C-peptide levels were not measured due to the lack of availability of this assay in all regions of the country, as it requires external processing. Antibody testing for anti-insulin antibodies by enzyme immunoassay (0.8 U/m) and anti-pancreatic islet antibodies (0.5 U/m) was negative. Genetic testing was performed using a targeted clinical exome for neonatal diabetes, which identified a novel homozygous missense *INS* variant (c.3G>A, p.Met11Ile), classified as pathogenic according to American College of Medical Genetics and Genomics guidelines (NM_00101042376.3; rs397515521) Results were available at 12 months of age.

Discussion

Neonatal diabetes represents a heterogeneous group of monogenic disorders, with diverse clinical manifestations (3). Its symptoms are nonspecific and include tachypnea, lethargy,

irritability, dehydration, failure to thrive, polyuria, convulsions, or hypotonia (9). Biochemical alterations that suggest the diagnosis include glycosuria, ketonuria, and hyperketonemia (4). The diagnosis in this patient was suspected when persistent hyperglycemia and high insulin requirements were noted. As part of the study, antibodies against pancreatic islets were requested; unfortunately, we could only obtain islet cell cytoplasmic antibodies (against cytoplasmic proteins in the beta cell) and anti-insulin, which results were negative.

The three main genes involved in permanent neonatal diabetes are *KCNJ11*, *ABCC8*, and *INS*, all located on chromosome 11. Pathogenic variants in the first two genes are the most frequent, accounting for 30 to 50% of all cases, and are responsible for encoding the subunits of the ATP-sensitive potassium channels of the beta cell (2,7,10). Pathogenic variants in the *INS* gene are mostly *de novo*, and their diagnosis is usually made before six months of age (7). However, some publications, such as that of Ngoc et al. (7), report later ages of diagnosis of 9.7 ± 1.9 months in up to 30% of cases.

Heterozygous missense variants in the *INS* gene have been associated with misfolding of the proinsulin molecule and consequently altered final insulin synthesis; these variants usually appear *de novo* in 80% of cases (3). Homozygous recessive pathogenic variants in this gene, as in our case, can impair insulin biosynthesis through mechanisms such as reduced mRNA stability, misfolding of proinsulin, and defective protein processing, leading to endoplasmic reticulum stress and β -cell apoptosis (2,3,7,9,11). Ngoc et al. (7) reported missense variants in exons 2, 3, and intronic region 2. In the present case, the location of the variant is in exon 2. It has been reported by *in silico* studies that the methionine residue at this position is at the start of protein translation, which is highly conserved between species and, therefore, supports its pathogenicity.

Other genes less frequently associated with neonatal diabetes are *SLC2A2*, *SLC19A2*, *EIF2AK3*, *GCK* (Glucokinase), *IPF1* (Insulin Promoting Factor), *PTF1A* (Pancreatic Transcription Factor Subunit 1 Alpha), *HNF1B* (Hepatocyte Nuclear Factor Homebox 1B), *FOXP3* (Forkhead Box P3), *ZFP57* (Zinc Finger Protein 57), *GLIS3* and *GATA6*. These genes should be considered in cases with a strong suspicion of NDM but with negative genetic studies for *KCNJ11*, *ABCC8* and *INS* variants (2,5,12).

Early genetic study is recommended when hyperglycemia persists longer than 2-3 weeks of life or when serum glucose levels greater than 1000 mg/dL are present without an apparent cause (5). In the present case, having hyperglycemia peaks higher than 500 mg/dL for more than two months of duration and high insulin requirements of up to 1.7 IU/kg/day made him a candidate for an early molecular study. However, his result was only available at around nine months of age.

Molecular testing by Next Generation Sequence or methylation-specific multiplex ligation-dependent probe amplification can provide a timely diagnosis to guide management and define prognosis (9,13). In the presented patient, since the results of the genetic panel were not available, a trial with sulfonylurea was performed, given that the most frequent cause of transient and permanent NDM involves the *KCNJ11* and *ABCC8* genes which are both responsive to treatment with sulfonylurea (3,13,14,15). The lack of response to treatment with oral medication suggested a different genetic etiology, which was corroborated by molecular testing.

Case series of patients with pathogenic variants for the *INS* gene report a higher prevalence of IUGR. This finding was corroborated in this child by anthropometric data at birth. IUGR is a common finding and is explained by *in utero* insulin deficiency, which is directly related to prenatal growth (16,17,18,19). In the long term, patients with NDM due to *INS* may present a risk of low weight, as is the current case, or low height, for which it is important to optimize glycemic control (20).

Glycemic control and insulin management are a challenge in neonatal diabetes. Newborns have an irregular amount and frequency of food intake that makes glycemic control less stable. The use of continuous glucose monitoring has been described as a method to guide insulin management and maintain blood glucose values within the normal range for a longer time (21). In clinical studies, continuous glucose monitoring has been described as safe, although with some technical limitations due to the small subcutaneous area available for sensor application in newborns and infants, especially those with low weight or poor fat accumulation, as well as increased risk of infection at the application site and local skin reactions that can be minimized by rotating the sensor sites (20,21,22). Despite being a useful tool, its use in children under two years of age is not authorized in our country, which limited this patient's access to this technology. It would have been particularly beneficial, as the patient may have experienced inadvertent hypoglycemia suggested by low glycated hemoglobin levels that could not be detected by the blood glucometer used in this case.

Finally, in neonates it is recommended to start with preprandial short-acting subcutaneous insulin at doses of 0.1-0.15 IU/kg/dose or guided by the response to insulin infusion (22). In this case, it is striking the high doses of insulin required during the first months of life (up to 1.77 U/kg/d), but with a progressive decrease in the requirements, reaching a dose of 0.7 U/kg/d at 18 months of age. Studies such as the one carried out in the Vietnamese population report insulin requirements at lower doses, with the highest insulin need reported at 1.1 U/kg/d, and this may be due to either genetic variability and/or clinical heterogeneity (7).

Conclusion

Neonatal diabetes is a rare condition with transient, permanent, and syndromic presentations.

This case highlights the necessity of early molecular diagnostics, which can inform personalized therapeutic strategies and improve long-term outcomes. In resource-limited settings, increased access to genetic testing may uncover previously unidentified mutations, contributing to global genetic databases and advancing our understanding of this rare condition. In this case, the novel homozygous variant in the *INS* gene highlights the complexity of NDM and the importance of ongoing research to refine treatment protocols and improve quality of life for affected individuals.

Ethics

Informed Consent: Informed consent was obtained from the parents to authorize the publication of this case. It was submitted for review by the Ethics Committee of the Medical School of the Universidad de Antioquia, Medellín, Colombia.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Vanesa Suarez, Gabriel del Castillo, Concept: Johana Andrea Botero Hernández, Gina González-Valencia, Design: Johana Andrea Botero Hernández, Gina González-Valencia, Data Collection and Processing: Gina González-Valencia, Vanessa Suarez, Analysis or Interpretation: Johana Andrea Botero Hernández, Gina González-Valencia, Literature Search: Johana Andrea Botero Hernández, Gina González-Valencia, Writing: Johana Andrea Botero Hernández, Gina González-Valencia, Vanessa Suarez.

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