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SCIENTIFIC LETTER

Neonatal diabetes onset mimicking an organic acidemia

Debut de diabetes neonatal simulando una acidemia orgánica

Neonatal diabetes mellitus (NDM) is a rare disorder (1/215,000–500,000 births). Its onset usually occurs during the first 6 months of life, even though some cases may appear in children aged up to 18 months of age.[1] It can be transient, with spontaneous resolution within the first weeks of life (median duration 12 weeks), or permanent. Permanent DM is associated with mutations in *KCNJ11*, *ABCC8* and *INS* genes in up to 53% of the cases.[2] *KCNJ11* and *ABCC8* genes code for the Kir6.2 and SUR1 subunits of the ATP-sensitive potassium (K-ATP) channel, which plays a central role in glucose-stimulated insulin secretion from the pancreatic β-cell.[3] This channel is involved in an essential step in insulin secretion. The channel consists of two types of essential subunits: the pore forming subunit Kir6.2 and the regulatory subunit sulfonylurea receptor 1 (SUR1) which is the target for sulfonylureas.

As NDM is a rare disorder, the diagnosis may be delayed. The prevalence of diabetes due to a mutation in *KCNJ11* is uncertain, between 34 and 64% patients with permanent diabetes.[3] Presentation with metabolic acidosis and hyperammonemia may be mistaken for an organic acidemia.

We present the case of a 3-month old female, born at term (37 weeks and 4 days) by emergent c-section delivery due to fetal bradichardia. Antenatal diagnosis of intrauterine growth restriction had been made in the 34th week of pregnancy, with a normal doppler birth weight was 2030 g (p2, −2.2 SD). Neonatal blood glucose was 72 mg/dl. Family history was unremarkable.

The baby presented with lethargy, tachypnea and feeding refusal. She had had cough and nasal congestion in the past few days without fever. On admission she had clinical features of ketoacidosis with Kussmaul breathing, mucous dehydration and compromised distal perfussion. On physical examination her heart rate was 199 bpm and her respiratory rate was 63 bpm. Her weight was 4.04 kg ($p < 1$, −2.4 SD), length 62 cm ($p70$) and head circumference 30.5 cm ($p2$). No dysmorphisms were observed.

Lab test revealed metabolic acidosis with high gap anion, hyperglycemia and ketosis. Venous blood pH was 7.04 and basses excess −23.3 mmol/L. Blood glucose was 844 mg/dl, ketonemia was 4 mmol/L and ketonuria was found. Serum ammonia was 288.9 μmol/L, and lactic acid was 10.9 mg/dL. Hyperglycemia was treated with intravenous fluids and continuous intravenous insulin perfusion. Ketoacidosis with hyperammonemia led to suspect an inherited metabolic disorder with organic acidemia so further diagnosis tests were performed and treatment for hyperammonemia was initiated (phenylbutyrate, L-arginine, n-carbamyl-glutamate).

Euglycemia was achieved within the first 12 h. Intravenous insulin perfusion was adjusted with capilar glucose values. C-peptide levels were 0.11 ng/ml.

Hyperammonemia was decreasing within the first 24 h. Treatment for hyperammonemia was interrupted within 60 h with normal values of ammonia (11.0–32.0 μmol/L). Diagnostic tests for organic acydemias and inherited metabolic disorders were negative (aminoacid and organic acid levels in blood and urine).

With the suspected diagnosis of neonatal diabetes, intravenous insulin perfusion was switched to continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring were initiated (Medtroning 640G integrated system®). The patient was discharged home and follow-up showed good metabolic control.

A sequence analysis of the coding and intronic and exonic flanking regions of 12 genes related to neonatal diabetes was performed (Ampliseq custom panel/Ion Torrent™ PGM), which revealed heterozygosity for a ''de novo'' mutation in exon 1 of the *KCNJ11* gene. The mutation led to a substitution of guanine for adenine in position 149 (c.149G>A), which led to a substitution in the protein structure of the arginine in position 50 by glutamine (p.Arg50Gln). This mutation was previously described in association with neonatal diabetes both transient and permanent, with favorable response to sulfonylureas.[3] Genetic testing for both parents was negative.

The patient was readmitted to discontinue subcutaneous insulin infusion and initiate oral therapy with glibenclamide, once the mutation was confirmed and a glucagon test was performed. Oral glibenclamide was initiated at 0.1 mg/kg/d while the insulin dose was gradually tapered. Gliblenclamide was continued at 0.8 mg/kg/d divided into 2 dosis on discharge. Home monitoring of blood glucose indicated successful transition to sulfonylurea therapy. Treatment with sulfonylurea was whitdrawn at 14 months with good subsequent glycemic control until today. During the follow up the patient showed appropriate neurological development.

Both neonatal diabetes mellitus and organic acidemias can lead to ketoacidosis in the neonatal period.[4] Similar onset and clinical features may delay or mistake initial diagnosis and approach. Also similar laboratory findings are confounding to the clinician. Hyperammonemia may mislead the diagnosis of diabetic ketoacidosis as shown in this

case. According to the literature, ammonia levels may rise with hyperinsulinism resulting from mutations in the glutamate dehydrogenase linked mechanism for insulin secretion. Glutamate dehydrogenase is expressed in the pancreas and liver and catalyzes oxidative deamination of glutamate to a-ketoglutamate, resulting in ammonia production. High levels of leucine and glutamic acid were reported in patients during diabetic ketoacidosis, leucine being an allosteric activator of glutamate dehydrogenase.[5] Akanshka et al. hypothesize dual mechanisms for hyperammonemia in a 6-month patient who presented with similar clinical features as our index patient and with a final diagnosis of neonatal diabetes. Aminoacid and organic acid levels in our patients were tested, showing no abnormalities. The authors also hypothesize that the utilization of glutamate by the glutamate dehydrogenase may compromise its availability for n-acetylglutamate synthesis (activator of carbamylphosphate synthase in the urea cycle) resulting in an impairment in the urea cycle. In our index patient urea levels were slightly elevated for her age at admission with normalization within the first 24 h.

Heterozygous activating mutations in *KCNJ11*, which encodes the kir6.2 subunit of the pancreatic K-ATP channel cause both permanent and transient neonatal diabetes.[6] More than 90% of these patient respond to sulfonylureas.[7] Approximately 50% of neonatal diabetes have K-channel mutations and therefore can be switched to sulfonylurea therapy, with improvement in glycemic control and quality of life. All patients with diabetes diagnosed before 6 months of age should be screened for these mutations.[8]

Authors' contribution

A.E. Laso and R. Saez performed the research and wrote the paper. A.M. Prado, R. Diaz and A. Moreno reviewed the paper. All authors have read and approved the final manuscript. All authors are accountable for all aspects of the work.

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Conflict of interest

The authors declare no conflict of interest.

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