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A Recessive Mutation in the Insulin Gene in Neonatal Diabetes

Nenoatal Diyabette İnsülin Geninde Resesif Mutasyon

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Abstract

Neonatal diabetes mellitus (DM) is a persistent hyperglycemia occurring in the first 4-6 weeks of life that lasts more than two weeks and requires insulin for management. We report a case of a 23-day-old boy with neonatal diabetes due to recessive inheritance INS promoter C-331 C>A mutation accompanied by diabetic ketoacidosis (DKA). The hyperglycemia and ketoacidosis resolved by the 48th hour of treatment consisting of IV insulin and rehydration. Subsequently, insulin treatment was continued with neutral protamine Hagedorn (NPH) insulin. Neonatal DM due to genetic mutation may mimic sepsis and should be kept in mind for all newborns who present with shortness of breath, vomiting, and dehydration. *Turk Jem 2015; 19: 25-27*

Key words: Diabetes, neonatal, INS, mutation, diabetic ketoacidosis

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Özet

Neonatal diabetes mellitus (DM) yaşamın ilk 4-6 haftasında ortaya çıkan, 2 haftadan fazla devam eden ve tedavisinde insülin gereksinimi olan durumdur. Biz diyabetik ketoasidoz (DKA) tablosu olan, 23 günlük bir erkek yenidoğanda saptadığımız resesif kalıtım gösteren INS promoter C-331 C>A mutasyonunu bildiriyoruz. Hiperglisemi ve ketoasidoz, 48 saatlik IV insülin ve rehidratasyon tedavisi ile düzeldi. İzlemde, insülin tedavisi NPH insülin ile devam etti. Genetik mutasyona bağlı neonatal DM sepsisi taklit edebilir ve nefes darlığı, kusma, dehidratasyonu olan tüm yenidoğanlarda akılda tutulmalıdır. *Turk Jem 2015; 19: 25-27*

Anahtar kelimeler: Diabetes, neonatal, INS, mutasyon, diyabetik ketoasidoz

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

Introduction

Neonatal diabetes (ND) is a form of monogenic diabetes that occurs during the first 6 months of life. A recent study estimated its minimum incidence as 1 in 90 000 population (1). ND is clinically divided in two forms: transient ND (TND) and permanent ND (PND) which is caused by several genetic defects (2).

Mutations in KCNJ11, ABCC8, and insulin gene (INS) are the main causes of PND (2). KCNJ11 and ABCC8 encode the subunits of the ATP-sensitive potassium channel (K(ATP)) of the pancreatic β-cells. Loss of insulin secretion occurs due to activating mutations of these subunits (3). INS mutations are associated with PND and other clinical conditions such as type 1b diabetes, maturity onset diabetes of the youth (MODY), type 2 diabetes, and TND (4). Here, we report a case of PND due to recessive inheritance INS mutation accompanied by diabetic ketoacidosis (DKA).

Case Report

A 23-day-old boy was referred to King Abdulaziz University Hospital, with history of vomiting, shortness of breath and irritability for 3 days. He was a product of full term delivery, uncomplicated pregnancy and spontaneous vaginal delivery with low birth weight of 2.3 kg. The mother reported non-bilious, non-bloody vomiting 2-3 times per day, with no history of diarrhea, constipation, abdominal distention or jaundice. There was a history of shortness of breath with no cyanosis, apnea, cough, or sweating during feeding. The mother stated that baby was irritable, crying all night and the frequency of diaper changing increased. He was on both breastfeeding and formula feeding. There was no consanguinity between the parents. There was family history of type 2 DM in grandmothers (Figure 1).

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On physical examination, the baby was irritable with respiratory distress in the form of grunting, working allae nasai, suprasternal, subcostal and intercostals recession and Kussmaul breathing. Patient was moderately dehydrated with no dysmorphism.

His vitals showed heart rate of 172 beats/min, respiratory rate of 77 breaths/min with body temperature of 37.6 °C (axillary). Oxygen saturation was 98% on room air with blood pressure of 94/54 mmHg. First-line laboratory analyses are shown into Table 1 (1).

A diagnosis of DKA was made; the baby was referred to the intensive care unit and started on intravenous regular insulin (0.1 IU/kg/hour) and a rehydration solution. Hyperglycemia and ketoacidosis resolved after 48 hour of treatment. Breast feeding was resumed with feedings at three- hour- interval. Insulin treatment was continued with subcutaneous neutral protamine Hagedorn (NPH) (1 IU/kg/day) insulin.

Genetic testing using sequence analysis of the promoter of the INS gene (NM_000207.2), confirmed the diagnosis of recessively inherited ND due to homozygous mutation in gene INS located at promoter with DNA description c-331 C>A. Both parents were heterozygous for INS mutation, c.-331C>A. The c.-331C>A promoter mutation disrupts a transcriptional regulatory site and is likely to result in decreased insulin transcription and the risk that this couple's next pregnancy will be affected by ND is 1 in 4.

During the follow-up, his last blood glucose level was 5.2 mmol/L, his most recent HbA1c value was 4.2% which was unreliable due to presence of fetal hemoglobin. Currently, the patient is 2 months old and on NPH regiment.

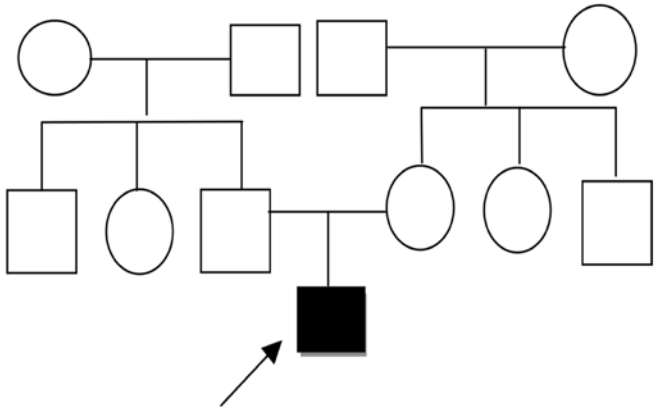

Figure 1. Squares represent male family member, and circles represent female member. Solid squares represent persons with diabetes carrying the mutation

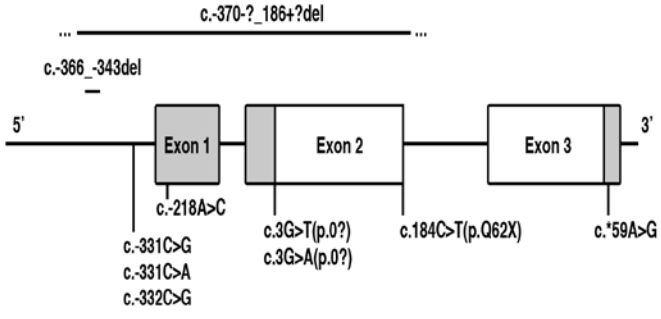

Figure 2. A schematic of the INS gene showing the 10 mutations identified. Point mutations are indicated below the exons, while deletions are shown above the gene. The blue shaded regions are noncoding, the red text indicates a deletion, the blue text are noncoding mutations, and the green are coding mutations. The precise breakpoints of the multiexonic deletion are not known; the solid line represents the minimal deleted region. Mutation nomenclature is based on the coding sequence where nucleotide 1 represents translational start site (10)

Discussion

ND is a rare entity that may present with non specific sepsis-like symptoms including grunting, shortness of breath, tachypnia, lethargy, irritability and jaundice.

ND includes transient (TND) and permanent (PND) forms, which have different molecular pathogenesis and insulin dependency (5). Intrauterine growth restriction has been reported in PND associated with recessive INS mutations (6). Our baby had homozygous INS promoter mutation (C-331 C>A), and his birth weight was 2.3 kg on the 3rd centile with high possibility to be PND.

Mutations in KCNJ11 and ABCC8 which encode for the two subunits of ATP-sensitive potassium channel (KATP) of the pancreatic beta cell which accounts for 50 and 10% of all cases of PND, respectively. Dominant mutations in the insulin gene (INS) are frequently found in patients with PND which account for 15-20% of all cases (Figure 2) (7). Despite these advances, the etiology of ND is still not known in 30% of patient with PND (8), suggesting other genetic (syndromatic) causes such as Wollcott-Rallison syndrome (AR), phosphoribosyl-ATP pyrophosphate hyperactivity (X-linked), and glucokinase deficiency (MODY2) and immune dysregulation, polyendocrinopathy, nenteropathy, X-linked (IPEX) syndrome (8).

Table 1. Laboratory results on presentation

Tests	Results	Reference
Serum glucose	48.2 mmol/L	3.8-6.6
Serum sodium	122 mmol/L	136-145
Serum chloride	59 mmol/L	98-107
Serum potassium	3.1 mmol/L	3.5-5.1
Blood urea nitrogen	7.9 mmol/L	2.5-6.4
Serum creatinine	89 Umol/L	53-115
Venous Blood Gas	PH: 7.023 HCO3: 4 meq/L PCO2: 15 mmHg BE: -25	7.34-7.45 18.5-24.5 32-48
Blood Culture	No growth	
insulin level	0.2 mIU/L	3-17
Peptide-C	0.183 nmol/L	0.37-1.47
Lactic acid	1.4	0.4-2
urine analysis	Specific gravity: 1.028 Glucose: +4 Ketones: +3	
urine culture	No growth	

In recessive mutations, diabetes occurs as a result of decreased insulin biosynthesis through several mechanisms, including gene deletion, lack of the translation initiation signal, and altered mRNA stability because of disruption of a polyadenylation signal (6). A subset of recessive mutations caused abnormal INS transcription, including the deletion of C1 and E1 cis regulatory element, or three different single base-pair substitution in a CC dinucleotide sequence (6) as in our patient with mutation in C-331 C>A.

Patient with recessive INS are diagnosed earlier (median 1 week vs. 10 weeks) and have lower birth weight compared to those with dominant INS mutations (6).

Insulin therapy is crucial in TND and some cases of PND to obtain optimal weight gain and growth in those infants.On the other, hand PND due to mutation in KCNJ11 or ABCC8 usually respond to sulfonyleurea (6,8,9).

In conclusion, recessive mutations in INS are a rare cause of ND and should be suspected in every patient presented with picture of neonatal sepsis.

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