Case Report

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Transient neonatal diabetes mellitus: a case report

Geçici neonatal diyabetes mellitus: bir olgu sunumu

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Abstract

Neonatal diabetes mellitus (NDM) is defined as hyperglycemia in the first six months of life for at least two weeks and requiring insulin therapy. Although its incidence is 1 in 90000-160000 live births, its frequency rises to 1/30000 in societies such as our country, where consanguineous marriages are common. NDM may be seen as transient (50-60%), permanent or a part of syndromes. Clinical manifestations of NDM are intrauterine growth retardation, growth cessation, excessive urination, dehydration, and ketoacidosis.

Since hyperglycemia may develop due to many different reasons in premature or low birth weight babies, difficulties and delays may occur in diagnosis. If the high blood glucose level lasts longer than 7-10 days after excluding other causes of transient hyperglycemia, it is recommended to suspect NDM and perform genetic examination, especially in infants with blood glucose above 250 mg/dL.

Herein, a newborn, referred to our neonatal unit due to persistent hyperglycemia on the postnatal 15th day and diagnosed as transient NDM after excluding other causes of hyperglycemia, is presented due to the rarity of the disease.

Keywords: Congenital, neonatal diabetes mellitus, transient, diagnosis.

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Öz

Neonatal diyabetes mellitus (NDM), yaşamın ilk altı ayında en az iki hafta süren ve insülin tedavisi gerektiren hiperglisemi olarak tanımlanır. Görülme sıklığı 90000-160000 canlı doğumda bir olmasına rağmen ülkemiz gibi akraba evliliklerinin yaygın olduğu toplumlarda görülme sıklığı 1/30000'e kadar çıkmaktadır. NDM geçici (%50-60), kalıcı veya sendromların bir parçası olarak görülebilir. NDM'nin klinik belirtileri intrauterin büyüme geriliği, büyümenin durması, aşırı idrara çıkma, dehidratasyon ve ketoasidozdur.

Prematüre veya düşük doğum ağırlıklı bebeklerde birçok farklı nedene bağlı olarak hiperglisemi gelişebileceğinden tanıda zorluklar ve gecikmeler yaşanabilmektedir. Geçici hipergliseminin diğer nedenleri dışlandıktan sonra kan şekeri yüksekliği 7-10 günden uzun sürüyorsa özellikle kan şekeri 250 mg/dL'nin üzerinde olan bebeklerde NDM'den şüphelenilmesi ve genetik inceleme yapılması önerilir.

Burada postnatal 15. günde inatçı hiperglisemi nedeniyle yenidoğan ünitemize başvuran ve diğer hiperglisemi nedenleri dışlandıktan sonra geçici NDM tanısı alan bir yenidoğan, hastalığın nadir görülmesi nedeniyle sunulmaktadır.

Anahtar kelimeler: Konjenital, neonatal diyabet, geçici, tanı.

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Introduction

Neonatal diabetes mellitus (NDM) is defined as hyperglycemia in the first six months of life, persisting for at least 15 days, and requiring insulin therapy [1-3]. A blood glucose level of >150 mg/dL in newborns is defined as hyperglycemia. Hyperglycemia is common, especially in premature and low-birth-weight infants, due to stress, sepsis, and the use of drugs such as steroids and beta-adrenergic agents [1, 4]. After excluding the other causes of transient hyperglycemia, NDM should be suspected in infants whose blood glucose level is still high, especially in infants whose blood glucose level is above 250 mg/dL [1, 4, 5]. Although the frequency of NDM is reported as one in every 90000-160000 live births, its frequency increases in societies where consanguineous marriages are common [1, 6]. In a study covering 5 provinces in the Southeastern Anatolia region of our country, the incidence of NDM was found to be at least 1/30000 [7].

Clinical findings of neonatal diabetes are failure to gain weight, growth retardation, excessive urination, and secondary dehydration. If the diagnosis is delayed, severe ketoacidosis may also be added to these symptoms [8]. The birth weight of babies is generally low due to intrauterine insulin deficiency [9]. NDM can be transient, permanent or a part of syndromes. Transient NDM is present in 50% to 60% of cases with neonatal diabetes [1, 8]. Transient NDM goes into remission in the first 3-6 months of life, but recurrence may be seen in 40-50% of cases, especially during puberty, so it is recommended not to exclude infants from clinical follow-up. Clinically, it is very difficult to distinguish between transient and permanent diabetes. More than 20 genetic causes have been reported for transient or permanent NDM [1, 6]. Insulin is the essential therapy for neonatal diabetes, and an infusion pump is often used in insulin therapy because of the low-dose insulin requirement in newborns [1, 10]. Although rare, oral sulfonylurea therapy is also used in some types of NDM [11, 12].

In this article, a newborn, referred to our neonatal unit due to persistent hyperglycemia on the postnatal 15th day and diagnosed as transient NDM after excluding other causes of hyperglycemia, is presented because of its rarity.

Case report

The patient, born at 37 weeks' gestation to a 26-year-old mother, had respiratory distress and was admitted to the neonatal intensive care unit with the preliminary diagnosis of transient tachypnea of the newborn. After the therapies of appropriate parenteral fluid (60 mL/kg/day, 10% dextrose, 4.2 mg/kg/minute glucose infusion) and nasal continuous positive airway pressure, the respiratory symptoms of the patient were resolved completely on the second day. Enteral nutrition was started with breast milk on the first postnatal day.

According to the patient history, hyperglycemia (825 mg/dL) was detected on postnatal first day, and also it was observed that hyperglycemia (735 mg/dL) persisted despite appropriate fluid therapy (80 mL/kg parenteral 5% dextrose, 2.4 mg/kg/minute, and enteral nutrition). In addition, although the patient had normal blood gases, negative keton in the urine, and reduction of glucose infusion, its blood glucose level was higher than 250 mg/dL. Therefore, it was decided to start the insulin infusion at a dose of 0.01 U/kg/h; afterwards, the insulin dose was increased to 0.07 U/kg/h. The patient, whose glucose levels were regulated after insulin therapy and whose hyperglycemia recurred when insulin therapy was interrupted (>250 mg/dL), was admitted to our neonatal intensive care unit (NICU) with a prediagnosis of neonatal diabetes for further examination and therapy.

It was learned from the patient's history that her parents were first-degree cousins, and they did not have a known disease such as diabetes. In addition, the patient's mother did not use any medication during pregnancy. On physical examination, the patient's body weight was 1945 grams (<3 percentile), head circumference was 33 cm (10 percentile), and height was 47 cm (3-10 percentile). Her general condition was good; she was active, and her system examinations were normal. She was externally female and did not have a syndromic facial appearance. In the laboratory evaluation, electrolytes and kidney

and liver function tests were normal; acute phase reactants were negative. The patient, who was considered small for gestational age (SGA), had negative TORCH serology. Blood glucose level was 462 mg/dL, C- peptide was 0.08 ug/L (N:0.9-7.1 ug/L), insulin was 2.3 mU/L (N:2.6-24.9 mU/ L), urine ketone was negative, urine glucose was 2 positive, anti-insulin antibody, anti-glutamate decarboxylase (anti-GAD) and islet cell antibodies were negative. The patient's stool steactocrit value was 0.014%, and pancreas was seen to be structurally normal on magnetic resonance imaging. In consultation with the genetics department, an examination was performed for neonatal diabetes genes, but no known mutations were detected.

A sensor-assisted insulin pump was fitted to the patient on the second day of hospitalization in the NICU. Basal insulin was determined to be 0.025 u/h (0.012 u/kg/h), the insulin sensitivity factor was 300 mg/dL, and the carbohydrate/ insulin ratio was 45/1. She was fed orally with breast milk every three hours. If the pre-feeding blood glucose level was above 150 mg/dL, a bolus wizard was used, and if it was below, a manual bolus was administered (0.15U for 100-150 mg/dL, 0.10U for <100 mg/dL). If the blood glucose level was below 60 mg/dL, no insulin was administered. Postprandial blood glucose was measured 1.5 hours after feeding, and a correction insulin dose was administered with a bolus wizard at values of blood glucose above 300 mg/dL.

On postnatal day 57, it was observed that the patient's insulin requirement started to decrase. On postnatal day 59, the patient no longer needed insulin, and her blood glucose level was in the normal range (between 70-100 mg/dl). The patient, whose blood glucose was regulated and did not require insulin, was discharged on postnatal day 62 with a diagnosis of transient NDM, and clinical follow-up was planned.

Discussion

Neonatal diabetes can be recognized in the first few days of life, and it may be difficult to diagnose, especially in premature or low-birth-weight babies, as hyperglycemia may develop due to many different reasons [9]. The prevalence of hyperglycemia in premature infants is 25-75%. Hyperglycemia is often seen in the first days of life and usually returns to normal levels after a few days [13]. There are many causes of hyperglycemia in the neonatal period, such as parenteral glucose administration, sepsis, increased regulatory hormones due to stress, and drugs like steroids [2-4]. Diabetes should be suspected in a newborn if hyperglycemia lasts longer than 7-10 days, and genetic examination should also be recommended if it exceeds 2-3 weeks [1, 5]. In the examinations of our patient for the causes of transient hyperglycemia, acute phase reactants were negative, and blood and urine cultures showed no growth. On the 15th day, she was followed up with the diagnosis of NDM because her hyperglycemia continued and her insulin need continued.

Neonatal diabetes mellitus may be presented with growth retardation, dehydration, and ketoacidosis, which may be fatal if the diagnosis is delayed [5, 6, 14]. Severe hyperglycemia (blood glucose >360 mg/dl) may cause significant osmotic changes leading to intraventricular bleeding [5]. It is very important to measure serum glucose, urine ketone, serum c- peptide, and insulin levels in the initial evaluation of infants with suspected of having this disease. Radiological evaluation of the pancreas should be recommended for the presence or absence of the pancreas, because this will guide the diagnosis and treatment [5, 10, 15]. Our patient had a low birth weight, but normal growth was achieved by insulin therapy, and laboratory values were also compatible with NDM. No structural anomaly or agenesis was detected in the pancreas radiologically with an MRI.

Neonatal diabetes is detected frequently in the first 6 months of life, but rarely until the 12th month of life, and it is highly likely to be caused by a monogenic defect [6, 16]. Genetic mutations cause NDM development by disrupting pancreatic beta cell functions, leading to decreased insulin secretion, pancreatic hypoplasia/agenesis or beta cell damage [15, 17]. Therefore, genetic examination is recommended in all NDM cases [6, 17]. In a large international cohort study including patients clinically diagnosed with neonatal diabetes; it was reported that 80% of the patients had an underlying genetic defect. It has also been reported that genetic analysis should be performed regardless of time in patients presenting with acute severe hyperglycemia

(serum glucose higher than 1000 mg/dL) [1, 5, 14]. So, we analyzed the genetic mutations of the patient for NMD by next generation sequence analysis; however, no known mutations could be detected.

Neonatal diabetes may be divided into transient, permanent, and syndromic forms according to its phenotypic characteristics [1]. Duplication of genes (ZAC, HYMAI) in the 6q24 region is responsible for the majority of the transient forms. Mutations of *the KCNJ11* and *ABCC8 genes,* which encode the potassium channel subunit of the beta cell responsible for insulin secretion, are in the second frequency range. In transient NDM, remission is usually between 13-18 weeks; however, in about 40% of the cases, hyperglycemia may recur in later life. Mutations of *KCNJ11, ABCC8*, and insulin *(INS) genes* are responsible for the permanent form of NDM. The genotype-phenotype relationship is weak, and it is difficult to distinguish the transient/permanent form clinically [1, 16]. Remission was developed in our patient between 8-9 weeks, and no genetic mutation was detected.

Early diagnosis and initiation of insulin therapy are very important in terms of the metabolic effects of ketoacidosis and preventing the development of chronic and irreversible complications of diabetes [1]. If the blood glucose level is higher than 180-200 mg/dL and there is +2 glucosuria in a newborn, insulin therapy should be needed [18]. The prognosis and treatment options for monogenic forms of neonatal diabetes vary greatly depending on which gene is affected. 40% of neonatal diabetes patients have mutations in KCNJ11 and ABCC8 that affect the pancreatic beta cell K-ATP channel [19]. Patients with these mutations can be treated with oral sulfonylureas. Studies show that, unlike insulin, early sulfonylurea therapy may improve neurodevelopmental outcomes in sulfonylurea-responsive patients [11, 12, 20]; however, without genetic conclusions, empirical sulfonylurea therapy is not recommended. Insulin therapy was started for our patient. Insulin therapy was administered with an infusion pump, as it provided ease of administration at very low doses. While insulin therapy is administered with an infusion pump, a blood glucose sensor is simultaneously placed subcutaneously, and continuous blood glucose is monitored. No severe symptomatic hypoglycemia was experienced in the clinical follow-up. The presented patient's blood glucose was regulated between 8 and 9 weeks; she did not need insulin therapy on the 62nd day, so she was discharged with the consideration of transient NDM and followed up clinically.

In conclusion, if hyperglycemia in the newborn exceeds one week, neonatal diabetes should be suspected; if it exceeds two weeks, molecular genetic studies should be started; and it should not be forgotten that early diagnosis and treatment have very important effects on the clinical course of these infants with NDM.

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Consent to participate: The authors certify that they obtained all the appropriate patient consent forms. The patient's mother and father provided their consent for the patient's images and other clinical information to be reported in this journal. The patient's mother and father understand that the patient's name and initials will not be published, and that although due effort has been made to conceal the patient's identity, anonymity cannot be guaranteed.

Authors' contributions to the article

S.A.A., O.M. and A.O. constructed the main idea and hypothesis of the study. D.Y. and M.O. developed the theory and arranged/edited the material and method section. G.O.C. and H.E. have done the evaluation of the data in the results section. Discussion section of the article was written by G.S.D., O.M.A.O. and G.S.D. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.