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Case Report

A Case of Neonatal Diabetes Presentation, Diagnosis and Management

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Abstract

We present a case of neonatal diabetes with special focus on the diagnostic therapeutic and education problems faced by the pediatric endocrinology team (physicians, nurses and diabetes educators) during the hospital course.

Keywords: NDM: Neonatal Diabetes Mellitus

Introduction

Neonatal diabetes mellitus (NDM) is an extremely rare presentation of diabetes. Affected infants are often found to be hyperglycemic (but rarely ketotic). Once considered a single disease, neonatal DM is now known to be caused by mutation affecting insulin synthesis and release, and by several mutations causing severe insulin resistance. Knowing the cause is important to selection of appropriate therapy. The therapy is also different from the typical pediatric because of size and diet. Training the family to care for the diabetic neonate is challenging for all. This case report will review the presentation, work up needed to reach the diagnosis, and the management plan and goals.

Case Report

A preterm male infant was born at 37 weeks' gestation, weighing 1565 grams. His mother is a 25 year old G2P0010. The mother denied any history of diabetes. The baby's parents were first cousins of Pakistani origin. Her pregnancy was complicated by intrauterine growth retardation (IUGR) and low amniotic fluid index score (AFI). Labor was induced because of severe IUGR.

The APGAR scores were 8 at 1 minute and 9 at 5 minutes. Patient was admitted to the neonatal intensive care unit because of the severely wasted appearance. On physical examination at birth, temperature was 96.5°-97.1° F, heart rate 118, respiratory rate 31, and blood pressure 83/48. The patient was very pale with light skin; the head was normocephalic without deformities. Cardiovascular and respiratory examinations were normal. The abdomen was soft, not distended, with a 3 vessel cord. The genitourinary examination showed bilateral descended testicles. The neurological examination showed excellent tone. Weight, length and FOC were below 3rd percentile.

Initial glucose levels were 85,81,91 mg/dl

Initial documented central glucose level was 175 mg/dl, but at 24 hours of life patient started having hyperglycemia with central glucose measurements of 697 and 843 mg/dl. At the age of 25 hours, an insulin drip was started at 0.1 units /Kg/h and the pediatric endocrinology team was consulted.

I – Medical Workup

A. Laboratory work

- Central glucose level: The first three levels were 175-697-843 mg/dl
- Insulin level (obtained after starting insulin drip) was 0.5 IU/ml at day 2 of life (normal fasting range 2-13 iu/ml)
- C-peptide levels (obtained after starting insulin drip) was 0.02 ng/ml at day 2 of life and less than 0.05 ng/ml at day 4 of life (normal levels 0.5-2.7 ng/ml)
- Lipid panel, liver enzymes, electrolytes were normal
- Hemoglobin A1C level obtained at day 29 of life was 6.3 %

B. Radiology Studies

Abdominal ultrasound showed no pancreatic abnormalities.

C. Genetic Testing

The neonatal diabetes mellitus by Athena Diagnostic was obtained. This test can detect mutations (point mutations, deletions, insertions and re-arrangements) in the coding sequences of the most common genes that are known to cause this condition including:

Glucokinase (GCK)

Potassium channel J11 (KCNJ11)

ATP-binding cassette transporter subfamily C member 8 (ABCC8)

Insulin (INS)

Insulin promoter factor 1 (IPF1)

The methodology uses Polymerase Chain Reaction (PCR), DNA sequencing of entire protein coding regions of genes.

The result of this DNA sequencing of the most common genes causing neonatal diabetes (IPF1, GCK, KCnJII and ABCC8) was unremarkable. However, a homozygous intronic mutation was found in the insulin gene:

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	Gene	Technical result	Mutation type	Inheritance
VUS	INS	C-188-15 G > A	Homozygous Intronic	Autosomal

No other abnormal variants were detected. Therefore, this was assumed to be the cause of neonatal diabetes. The parents were offered testing for the same mutation but declined.

II – Management plan and goals

At the seventh day of life, patient started feeding on breast milk with some added formula (Neosure 22). He was able to feed every 3 hours. At that time we changed the insulin therapy from the insulin drip to basal bolus subcutaneous insulin synchronized with feeds, as follows:

1. Insulin glargine (r DNA origin) 0.25 units daily
2. Insulin lispro 0.25 units every six hours (every other feeds) for glucose levels 300-450 mg/dl and 0.5 units for glucose levels above 450 mg/dl

The hospital pharmacist was able to dilute insulin to reach low concentration. Each 1 ml insulin was diluted with 3 ml of normal saline before each dose with estimated viability of 1 hour.

The blood sugar was tested prior to each feed. Short acting insulin dose was not given when blood sugar was below 100 mg/dl. The baby had few hypoglycemic episodes that were corrected by glucose infusions. There was no seizure episodes related to hypoglycemia. Continuous Glucose Monitoring Sensor (CGMS) was considered to monitor fluctuations in blood sugar, but lack of ample subcutaneous fat precluded the stability of the sensor's needle. The aim of the therapy was to treat hyperglycemia while preventing hypoglycemia episodes. Blood glucose was kept in the range of 150-200 mg/dl.

At two months of age, the patient had gained weight (3.35 kg), had increased subcutaneous fat and was requiring a larger daily dose of long acting insulin (total dose of 2 units per day). The patient was discharged home at the age of two months with scheduled follow-up in 1 week.

The major obstacles in treating neonatal diabetes mellitus that we faced were:

1. Difficulty in preparing very low dose insulin. Most of the manufacturers of commercially available insulin advise against any form of dilutions to prevent any possibility of dysfunction. We had no other choice.
2. Difficulty with insulin administration in a very thin newborn with lack of subcutaneous fat tissue. Intramuscular insulin injection may also cause erratic insulin absorption
3. Difficulty in predicting milk intake. Like any normal newborn, feeding may be variable. The patient experienced hypoglycemic episodes on days that he was not able to finish or tolerate his feeds.
4. Consequences of multiple blood sticks to test blood sugar and frequent blood draws that could theoretically cause anemia. We have adhered to our hospital protocol to prevent this from occurring.
5. Physical and psychological factors that affected the family members of the patient on daily diabetes management.

Discussion

Incidence

Neonatal diabetes mellitus (NDM) is an extremely rare presentation of diabetes. The National Institute of Health (NIH) estimates the incidence of NDM between 1 in 100,000 to 1 in 500,000 live births. [1] Varying by region.

An Italian study reported an incidence of 1 in 90,000 live births in Italy [2]. Since the condition is usually caused by a single gene mutation, it is expected to have a higher incidence in geographical regions with high rates of consanguinity, as was seen in our subject family.

Types

Initially neonatal diabetes seemed divided in two types: Transient (TNDM) and Permanent (PNDM). This classification clearly depends on the duration and progression of the condition [3]. In almost 50% of the cases, NDM is transient disappearing in infancy with possibility of recurrence later on in life. In the other half, NDM is permanent.

NDM should be differentiated from other causes of hyperglycemia in the newborn including iatrogenic causes, stress and insulin resistance [4]

NDM should be differentiated also from type 1 diabetes mellitus (autoimmune) that may start at early infancy (as early as 6 months of age) [1]. Type 1 diabetes is almost always associated with positive immune markers for diabetes (Table).

Table: The following **table** demonstrates the classification and approach to neonatal hyperglycemia:

Neonatal Hyperglycemia						
Latrogenic Stress	Neonatal Diabetes Mellitus (NDM)					
	Transient TNDM	Recurrence	Permanent PNDM			
			Negative Immune markers Early presentation			Positive Immune Markers Age after 6 months
			Syndromic form		Specific Genetic Mutation	
			Congenital Lipodystrophy	Lnsulin Resistance	Common / Rare	Type 1 diabetes mellitus
					KCNJII GCK ABCC8 IPF1 / INS FOXP3 ZPF57 EIF2AK3 SLC2A2	

Diagnosis

Persistent hyperglycemia, insulin deficiency (low insulin and C-peptide levels) are common features in making the diagnosis. Lack of immune markers for type 1 diabetes may be deceiving for late onset presentation. The most important aspect of the confirming the diagnosis is molecular genetic testing. There are more than a dozen genes/loci associated with neonatal diabetes [5-9].

Some examples of the known mutations causing neonatal diabetes are: [5]

Glucokinase (GCK)

Potassium channel J11 (KCNJ11)

ATP-binding cassette transporter subfamily C member 8 (ABCC8)

Insulin (INS)

6q24, solute carrier family 2A2 (SLC2A2)

SLC 19 A2, eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3)

Insulin promoter factor 1 (IPF1)

Pancreas transcription factor 1 subunit alpha (IPF1A)

Hepatocyte nuclear factor 1 homeobox B (HNF1B)

Forkhead box P 3 (FOXP3)

Zinc finger protein 57 (ZFP57)

The prevalence of these mutations can vary from one region to another worldwide [5,10] but KCNJII, ABCC8, GCK and IPF1 are the most commonly reported.

Genetic testing may play a very important role in transferring therapy from insulin to sulfonylurea since patients with certain mutations in the pancreatic ATP sensitive K+ channel proteins like the sulfonylurea receptor 1 (SUR1) and inward rectifier K+ channel Kir 6.2 (Kir 6.2) may respond well to sulfonylurea therapy [10-13] instead of insulin.

There are some syndromic forms of neonatal diabetes described like Berardinelli-Seip Syndrome [14], associated with insulin resistance and congenital lipodystrophy and Wolcott-Rallison Syndrome [15] associated with multiple epiphyseal dysplasia, osteopenia, mental retardation and hepatic and renal dysfunction.

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