Neonatal Diabetes Mellitus

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INTRODUCTION

The Diabetic Syndrome, characterized by hyperglycemia and glucosuria with or without ketonuria, is rarely found in children under one year old.

Neonatal Diabetes Mellitus is a rare disorder that appears at neonatal age.

Two types have been described in literature based upon the duration of insulin dependency.

Recently, various genetic mutations have been identified associated with NDM.
OBJECTIVES

- Definition and forms of Neonatal diabetes mellitus (NDM).
- Etiologies of neonatal diabetes.
- Appreciate the diagnostic, therapeutic and prognostic significance of neonatal diabetes mellitus.
CASE

- MRN 681546
- 40 days old  Yemini  boy
- He is product of term pregnancy delivered by a normal vaginal delivery, for booked mother.
- The antenatal period was normal.
- The birth weight was 1.7kg with symmetrical IUGR.
Family History:
- Healthy consanguineous parents .
- The first lonely baby .
- No history of abortion
- The family history was significant for diabetic in both grandparents .
- No history of NDM , IUGR or neonatal death in the family .
He was admitted to the neonatal intensive care unit for gaining weight.

There he was found to have high blood sugar level $>250$mg/dl no ketonuria.

Sepsis was ruled out.

Insulin therapy was started at NICU.

Feeding through NGT was started.

25 days later discharged on NGT feeding and neutral protamie hagedorn (NPH) insulin 1 unit per needed if blood glucose more than 250mg/dl.

Discharged weight was 1.7 kg (from the mother).
At home the boy stay around tow weeks during, his blood sugar still fluctuating between hyperglycemic and hypoglycemic attacks and failure to gain weight.

At age of 40 days the boy was seen in our pediatric endocrinology clinic as a referred case of poorly controlled blood sugar and admitted electively for control blood sugar level.
Physical examination on admission:

- Conscious, alert, mild dehydrated, not distress dysmorphic (overlapping 5th finger of both hand, triangular face, rocker bottom appearance? Trisomy 18)
- weight=1.5kg
- length=41cm, less than 5th centile
- head circumference=32cm
- Respiratory system normal breathing pattern with equal normal breath sounds.
- Cardiovascular system normal heart sounds, no other added sounds with good peripheral pulses and perfusion.
- Abdomen was slight distended, soft lax and palpable organ.
- CNS was normal examination including fundus examination.
Laboratory evaluations revealed complete blood count were normal.
Blood glucose was 200mg/DL
Blood gas was normal
HbA1c was 5.8% at presentation.
liver and renal profile were normal
The structural diseases of the pancreas were excluded by ultrasonography of the abdomen.
Echo was normal
Chromosomal study and DNA analysis still bending.
Pt admitted to PMW and started on:

- Continuous NGT feeding with caloric intake of 150 kcal/Kg/day
- Regular S.C injection of NPH as 1 I.U twice a day
- Regular monitoring of his blood sugar level and daily weight record.
- The boy was too sensitive to insulin injection and he had repeated attacks of hypoglycemia. The dose was tapered till he was receiving a dose of 0.1 I.U of NPH PRN if blood glucose more than 250mg/dl.
Later on therapy with oral sulfonylurea (Glibenclamide) was started with small dose of 0.1 mg / Kg once daily that gradually increased. The boy wt. was increased and reach 1.8 Kg although of that he still to show attacks of both hypoglycemia and hyperglycemia but less than before.

1/11 discharge on Glibenclamide 1mg twice a day and PRN 0.1 I.U NPH NGT feeding with follow up in endocrinology and genetic clinic.
FOLLOW UP

- seen in genetic clinic on 5/12.
- seen in endocrinology clinic on 20/12/2009 he still not gaining Wt (Wt. still 1.8 kg) his hyperglycemic attacks 2-3 times/week (mother was monitoring blood sugar of minimum 4 times/day all before feeding) no vomiting or diarrhea no abnormal movement only lower limb edema that increase and decrease.
Neonatal diabetes mellitus
The most common forms of diabetes, *type 1* and *type 2*, are polygenic. Meaning the risk of developing these forms of diabetes is related to multiple genes. Environmental factors also play a part in the development of polygenic forms of diabetes. Polygenic forms of diabetes often run in families.
Some rare forms of diabetes result from mutations in a single gene and are called monogenic. Monogenic forms of diabetes account for about 1 to 5 percent of all cases of diabetes in young people. Neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. MODY is much more common than NDM. NDM first occurs in newborns and young infants; MODY usually first occurs in children or adolescents but may be mild and not detected until adulthood.
In most cases of monogenic diabetes, the gene mutation is inherited; in the remaining cases the gene mutation develops spontaneously.

Most mutations in monogenic diabetes reduce the body’s ability to produce insulin, a protein produced in the pancreas that helps the body use glucose for energy.
NEONATAL DIABETES MELLITUS

Metabolic disorder characterized by insulin-requiring hyperglycemia within the first month of life.

It is a rare entity, with an estimated incidence of 1 in 400000-500000 neonates.

Most commonly is inherited in an autosomal recessive manner and less commonly in an autosomal dominant manner.
Can be either transient (TNDM) or permanent (PNDM).

In TNDM, diabetes develops within days after birth and resolves again within weeks or months, before recurring – in a milder form – in late childhood.

In PNDM, diabetes develops within days to months after birth and persists throughout life.
TNDM

- Represents 50% to 60% of cases of neonatal diabetes.
- Diabetes mellitus tends to develop in the first week of life.
- Diabetes lasts from two weeks to maximum one year of age.
- The need for insulin gradually declines.
- Intermittent episodes of hyperglycemia may occur in childhood, particularly during illnesses.
- Recurrence in adolescence is more with type 2 diabetes mellitus.
- Women during pregnancy at risk of gestational diabetes.
TNDM is caused by overexpression of a locus containing two imprinted genes, *PLAGL1 (ZAC)* and *HYMAI*, on chromosome 6q24. Normally the maternal copies of *PLAGL1 (ZAC)* and *HYMAI* are silent as a result of differential methylation of the promoter; thus, only one copy (the paternal copy) of *PLAGL1 (ZAC)* and *HYMAI* is expressed. In TNDM, two (or more) expressed copies of *PLAGL1 (ZAC)* and *HYMAI* are present through one of the three following mechanisms:

- **Paternal uniparental disomy of chromosome 6 (UPD6).** Two chromosome 6 homologues, each with an expressed copy of *PLAGL1 (ZAC)* and *HYMAI*, are inherited from the father and none from the mother.

- **Paternal duplication of 6q24.** This is usually a submicroscopic tandem duplication that results in the presence of two copies of *PLAGL1 (ZAC)* and *HYMAI* on the paternal chromosome 6.

- **A methylation defect in the promoter of *PLAGL1 (ZAC)/ HYMAI.*** Loss of methylation in the maternal copy of the promoter results in expression of the maternal copy of *PLAGL1 (ZAC)/ HYMAI.*
The cardinal features are:
- low birth weight due to severe intrauterine growth retardation
- failure to thrive
- hyperglycemia in absence of ketoacidosis
- frequent urination and dehydration
- lethargy, poor feeding
- Macroglossia and umbilical hernia are often present
Mean age of diagnosis of seven weeks. The course of PNDM is highly variable depending on the genotype. Clinical manifestations at the time of diagnosis include intrauterine growth retardation (IUGR); hyperglycemia, glycosuria, osmotic polyuria, severe dehydration, ketoacidosis and failure to thrive. Approximately 20% of individuals with mutations in \textit{KCNJ11} have associated neurologic findings called the DEND syndrome.
Five genes are currently known to be associated with nonsyndromic permanent neonatal diabetes:

- **KCNJ11.** Approximately 30% of PNDM is attributed to activating mutations of *KCNJ11*, the gene encoding one of the two components of the beta-cell plasma membrane ATP-dependent potassium channel.
- **ABCC8.** Approximately 19% of PNDM is attributed to activating mutations of *ABCC8*, the gene encoding the second of the two components of the beta-cell plasma membrane ATP-dependent potassium channel.
- **INS.** Approximately 20% of PNDM is attributed to mutations in *INS*, the gene encoding insulin.
- **GCK.** Rarely, PNDM is attributed to inactivating mutations of *GCK*, the gene encoding glucokinase (hexokinase IV).
- **PDX1.** Rarely, PNDM is attributed to inactivating mutations of *PDX1*. 

MOLECULAR GENETIC
The mode of inheritance of permanent neonatal diabetes mellitus (PNDM) varies by gene:

- Autosomal dominant: \textit{KCNJ11} and \textit{INS}
- Autosomal dominant or autosomal recessive: \textit{ABCC8}
- Autosomal recessive: \textit{GCK} and \textit{PDX1}
SYNDROMIC CAUSES OF PERMANENT NEONATAL DIABETES MELLITUS

- 1-PTF1A-related PNDM.
  - Homozygous inactivating mutations in \( PTF1A \) cause pancreatic agenesis leading to PNDM associated with cerebellar agenesis and severe neurologic dysfunction.

- 2-Immune dysregulation polyendocrinopathy and enteropathy, X-linked (IPEX) syndrome
  - Is characterized by the development of overwhelming systemic autoimmunity in the first year of life resulting in the commonly observed triad of watery diarrhea, eczematous dermatitis, and endocrinopathy seen most commonly as insulin-dependent diabetes mellitus. Inheritance is X-linked.
3-Wolcott-Rallison syndrome
- Is characterized by infantile-onset diabetes mellitus and exocrine pancreatic dysfunction (25%) as well as the extra-pancreatic manifestations of epiphyseal dysplasia (90%), developmental delay (80%), acute liver failure (75%), osteopenia (50%), and hypothyroidism (25%). Inheritance is autosomal recessive.

4-A syndrome of neonatal diabetes mellitus with congenital hypothyroidism
- Has been associated with mutations in GLIS3 the syndrome can present with congenital glaucoma, hepatic fibrosis, and polycystic kidney.
**DIAGNOSIS**

- *Clinical*
- History and clinical examination.
- *Testing*
  - ++Laboratory testing
    - Elevated levels of glucose in blood or urine.
    - Plasma insulin concentrations are low
  - Islet cell antibodies are absent.
- ++Pancreatic imaging
- ++Molecular Genetic Testing
Individuals with one parent with diabetes mellitus should first be tested for mutations in *KCNJ11* and then *ABCC8* and *INS* because these can be dominantly transmitted.

Individuals with neurologic findings suggestive of developmental delay, epilepsy, and neonatal diabetes mellitus (DEND) syndrome should first be tested for mutations in *KCNJ11*.

Individuals with two parents with diabetes mellitus should first be tested for mutations in *GCK* and *PDX1*, as carriers of these mutations can have mild diabetes mellitus (*GCK-MODY* and *PDX1-MODY*, respectively) with onset in adolescence or early adulthood.

Individuals with pancreatic insufficiency or agenesis should be tested for mutations in *PDX1*.

For individuals with syndromic PNDM, the extrapancreatic characteristics should guide genetic testing. Individuals with PNDM and:

+ Enteropathy and dermatitis should be tested for mutations in *FOXP3* (IPEX syndrome);
+ Cerebellar involvement should be tested for mutations in *PTF1A*;
+ Congenital hypothyroidism should be tested for mutations in *GLIS3*. 
Insulin therapy is crucial in NDM to obtain satisfactory weight gain and growth in newborns with intra-uterine growth retardation.

Although pediatricians face numerous difficulties in managing insulin therapy in the newborn period, very few data are available on the methods of insulin delivery in neonatal diabetes.

In general, rapid-acting and short-acting Insulin (except when used as a continuous intravenous or subcutaneous infusion) should be avoided as they may cause severe hypoglycemic events.

Blood glucose concentrations should be monitored at least four times a day lifelong to achieve the goals of therapy.
the American Diabetes Association recommends the following:

- Glycemic targets:
  - 100-180 mg/dL before meals
  - 110-200 mg/dL at bedtime/overnight
- Hemoglobin A1c value between 7.5% and 8.5%
Initial treatment. Rehydration and intravenous insulin infusion should be started promptly after diagnosis.

Long-term medical management
An appropriate regimen of subcutaneous insulin administration should be established when the infant is stable and tolerating oral feedings. Few data are available regarding the most appropriate insulin preparations for young infants.

- Intermediate-acting insulin preparations (neutral protamine Hagedorn [NPH]) tend to have a shorter duration of action in infants, possibly because of smaller dose size or higher subcutaneous blood flow.
- The newer, longer-acting preparations with no peak-of-action effect such as Lantus® (glargine) may work better in small infants.
Children with mutations in *KCNJ11* or *ABCC8* can be transitioned to therapy with oral sulfonylureas; high doses are usually required (0.4-1.0 mg/kg/day of glibenclamide).

High caloric intake should be maintained in these newborns and insulin therapy given.

Pancreatic enzyme replacement therapy is required in persons with exocrine pancreatic insufficiency.
Aggressive treatment and frequent monitoring of blood glucose concentrations is essential to avoid acute complications such as diabetic ketoacidosis and hypoglycemia.

Long-term complications of diabetes mellitus can be significantly reduced by maintaining blood glucose concentrations in the appropriate range.

- Yearly screening for chronic complications associated with diabetes mellitus should be started after age ten years and should include the following:
  - Screening for microalbuminuria
  - Ophthalmologic examination to screen for retinopathy
The prognosis is linked to the mutations as well the rapidity with which the disease is recognized and treated.

The prognosis rely on the metabolic control, which will determine the timing of appearance of the long standing diabetes complications.
SUMMARY

1) Very early onset diabetes mellitus seems to be unrelated to autoimmunity in most instances.
2) Considerable overlap occurs between the two groups, so that TNDM cannot be distinguished from PNDM based on clinical features.
3) Patients with TNDM are more likely to have intrauterine growth retardation and less likely to develop ketoacidosis than patients with PNDM.
4) TNDM patients are younger at the age of diagnosis of diabetes and have lower initial insulin requirements.

5) Recurrent diabetes is common in patients with "transient" neonatal diabetes mellitus and, consequently, prolonged follow-up is imperative.

6) Molecular analysis of chromosome 6 anomalies, provide a tool for identifying transient from permanent neonatal diabetes mellitus in the neonatal period.