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Neonatal Diabetes Mellitus

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Neonatal diabetes mellitus is a rare form of insulin dependent diabetes mellitus that present within the first month of life, lasting at least two weeks and requiring insulin therapy. Intrauterine growth restriction, failure to thrive, fever, dehydration, hyperglycemia and acidosis with or without ketonuria are the clinical features of the disease. We report four cases of neonatal diabetes mellitus; two of them had a transient course.

Key words: *Insulin, Neonatal Diabetes mellitus.*

Impaired glucose tolerance in neonates can be due to various factors including neonatal diabetes mellitus (NDM). Neonatal diabetes mellitus is a rare form of insulin dependent diabetes mellitus (IDDM) with an incidence of 1/400 000 that present within the first four weeks of life persisting for at least two weeks and requiring insulin treatment(1,2). The outcome is highly variable; may be either permanent, or transient with/without subsequent recurrence(3). We present four cases of neonatal diabetes mellitus; two of them had a transient course.

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Case Reports

Case 1

This term male neonate was the fourth child of non-consanguinous parents. The mother was 38 years old and pregnancy was complicated by severe oligohydramnios. His birth weight was 1860 g (<10th percentile) and length was 32 cm (10-25th percentile). The physical examination was normal. His brother had been diagnosed as IDDM when he was five years old.

On the 10th day of hospitalization, he had hyperglycemia (307 mg/dL) and was treated with subcutaneous crystalline insulin because of persistent high glucose levels. He was fed eight times a day with 120 kcal/kg/day. During hospitalization, he sometimes developed metabolic acidosis without ketosis requiring bicarbonate therapy. On the 26th day, subcutaneous isophane (NPH) insulin was started once daily. His insulin and C-peptide levels were 2.2 micCIU/mL (normal values 2.1-30.8 micIU/mL) and 0.2 ng/mL (normal values 1.1-3.2 ng/mL) respectively. Tests for intrauterine infections (TORCH) and islet cell antibodies were negative. He gained 30-50 g/kg/day of weight during hospitalization. On 44th day of hospitalization he was discharged on twice daily insulin regimen. However, his parents gave up insulin treatment after discharge and on follow up at 3 months of age

he was well and his blood glucose levels were within normal limits. He is now 3 years old and a well growing child.

Case 2

This female neonate was the first child of young consanguinous parents. Pregnancy was complicated by oligohydramnios and cesarean section was performed at 36 week gestation age. Her birth weight was 1200 g (<10th percentile) and length was 34 cm (<10th percentile). The physical examination was normal. Her grandmother and grand aunt have non-insulin dependent diabetes mellitus. On the 3rd day of life she had hyperglycemia (380 mg/dL) and was treated with subcutaneous insulin (0.1 U/kg). Her insulin and C-peptide levels were low, 2 micIU/mL and 0.1 ng/mL respectively. Intrauterine infection markers and islet cell antibodies were negative, HbAlc levels were normal. Between day 4 and 10 of life, she remained normoglycemic and did not require insulin treatment. Glucose levels were between 65-117g/dL. After 10th day of life, hyperglycemia reccured and insulin infusion (0.1-0.5 U/kg/h) was started.

Blood ketones were negative at hyperglycemic periods and she never developed acidosis. After 30 days, NPH insulin treatment was started. During treatment she had hypoglycemia with blood glucoce levels between 25-45 mg/dL and treated with enteral or parenteral glucose. She gained 30-60 g/kg/day with eight times feeding per day. She is now 2 years of age and on insulin glarjin 2 times a day. Her blood glucose and glycosylated hemoglobin levels are under control.

Case 3

The infant was a term, small for gestational age, male infant of consanguinous parents, admitted at 18 days of age. His growth parameters were 2250 g body weight (<10th percentile) and 50 cm length (50-75th percentile). On admission, he was in respiratory distress, acidotic, dehydrated and septic in appearence. Laboratory investigations demonstrated hyperglycemia (390 mg/dL), hypertriglyceridemia, severe metabolic acidosis, renal failure, and hypernatremia. His C-peptide level was 0.9 ng/mL. The problems were resolved with appropriate therapy and persistent hyperglycemia was treated with continuous intravenous (0.1.-0.7 U/kg/h) and subsequent subcutaneous insulin therapy. The insulin treatment was discontinued at 4 months of age. He is now 14 months old and blood glucose values are in normal range.

Case 4

This male infant was born severely growth retarded at 36 weeks of gestation to a gestationally diabetic mother. The parents were consanguinous. He was referred at 5 days of age for persistent hyperglycemia (410 and 380 mg/dL). His growth related parameters were 1300 g body weight (<10th percentile), 38 cm length (<10th percentile), and 29 cm head circumference (<10th percentile). On physical examination, he was not acidotic, had no clinical manifestations of hyperglycemia and dysmorphic features were not detected. He was treated with insulin but glucose control was erratic. Plasma C-peptide level was 0.57 ng/mL, insulin was 0.17 micIU/mL, islet-cell antibodies were negative and his glycosylated hemoglobin values were elevated. He is now 2½-years-old and on insulin glarjin once a day. He has good glycemic control but poor weight gain.

Discussion

Hyperglycemia, defined as fasting blood glucose greater than 125 mg/dL is mostly seen in very low birth weight infants receiving intravenous glucose infusion. Sepsis and stress can also be associated with hyperglycemia by catecholamines, cortisol influences on the

mobilization of glycogen, gluconeogenesis and insulin response. On the other hand, endotoxins may have a direct effect on insulin actions in septic infants. Transient and permanent diabetes mellitus have to be differentiated from the transient hyper-glycemia seen in neonates receiving parenteral glucose infusion and those with septicemia and central nervous system disorders(2). All of our patients were healthy, were not receiving parenteral nutrition and sepsis markers were negative.

Neonatal diabetes mellitus, an uncommon cause of hyperglycemia in the newborn period, presents within the first four weeks of life and persists for more than two weeks(3). Intrauterine growth retardation, failure to thrive, fever, dehydration, hyperglycemia, acidosis with or without ketonuria are the clinical features of the disease. Insulin secreted by the fetal pancreas has a significant role in growth and metabolism of the fetus during the last half of gestation. Intrauterine deficiency of insulin may be the cause of intrauterine growth retardation(4). All the patients reported here had intrauterine growth retardation and had low levels of insulin and C-peptide.

Etiology of NDM is unclear and its pathogenesis differs from insulin dependent diabetes mellitus in childhood because of its highly variable course. Presence of islet cell antibodies has not been reported in NDM(5). Absence of autoimmune markers typical for IDDM is also consistent with the diagnosis(4). Islet cell antibodies of the present patients were negative.

Neonatal diabetes mellitus, seems to form a distinct entity of inborn pancreatic malfunction(4). First phase of insulin release during the intravenous glucose tolerance test is a sensitive index of beta cell reserve; if there is a decreased first phase of insulin response, this is a good predictor of later development of diabetes mellitus(6). Most children with transient NDM in remission have no evidence of beta cell dysfunction or insulin resistance in the fasting state(7). In a study about half of the NDM patients developed permanent diabetes mellitus(3). Of the patients reported by von Muhlendahl, 26 infants had permanent diabetes, 18 had transient diabetes, and 13 had transient which diabetes recurred when they were 7 to 20 years old(3). Permanent NDM developed in 2 of the patients reported here.

Transient neonatal diabetes mellitus (TNDM) typically lasts for weeks and months requiring insulin therapy(8). Most of the cases of TNDM are sporadic but there are familial cases(9). Although they often have a permanent remission, they need to be closely followed as diabetes can recur(3). Several hypothesis concerning its etiology have been postulated, such as pancreatic immaturity, paternal uniparental isodisomy of chromosome 6 and the existence of a gene located in 6q22-23 chromosome region subjected to imprinting and exclusively of paternal expression(10-13). Unfortunately, paternal uniparental isodisomy could not be studied in these patients.

The cause of β-cell destruction in permanent cases is not yet known. Permanent NDM is uncommon and is usually due to a pancreatic dysgenesis often associated with other malformations (3,14-16). Giralt, *et al.*(15) described permanent diabetes of a neonate with hypothyroidism, bilateral sensorineural deafness, and bilateral congenital cataract. Kentrup, *et al.*(16) described a case of NDM with hypergalactosemia and Milenkovic, *et al.*(17) reported macroglossia, umbilical hernia, onychomycosis, inguinoscrotal hernia with TNDM. Our patients did not have any associated anomaly. The prognosis is different

in transient and permanent forms and it is difficult to distinguish these forms at onset.

In conclusion, NDM should be considered in the diagnosis of hyperglycemic and small for date infants. Close blood glucose monitoring is essential as long as hyperglycemia persists. Because recurrent diabetes is common in patients with transient NDM, prolonged follow up is imperative

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