

**Received:** 2012.03.19  
**Accepted:** 2012.05.13  
**Published:** 2012.07.10

## Permanent neonatal diabetes mellitus

**Abdulrahman Al-Matary<sup>1</sup>, Mushtaq Hussain<sup>1,2</sup>, Ahmed Nahari<sup>1,3,4</sup>, Jaffar Ali<sup>5,6,7</sup>**

<sup>1</sup> Department of Neonatology, King Fahad Medical City Riyadh, Saudi Arabia

<sup>2</sup> Neonatal ICU, Mid Western Regional Maternity Hospital, Ennis Road, Limerick, Ireland

<sup>3</sup> Pediatrics Department, King Fahad Medical City, Riyadh, Saudi Arabia

<sup>4</sup> King Fahad Central Hospital, Jazan, Saudi Arabia

<sup>5</sup> Research and Scientific Publications Center, King Fahad Medical City, Riyadh, Saudi Arabia

<sup>6</sup> Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

<sup>7</sup> Stem Cell Unit, Department Anatomy, King Saud University, Riyadh, Saudi Arabia

### Summary

#### Background:

Neonatal diabetes is a rare cause of hyperglycemia, affecting 1: 500,000 births, with persistent hyperglycemia occurring in the first months of life lasting more than 2 weeks and requiring insulin. This condition in infants less than 6 months of age is considered as permanent neonatal diabetes mellitus.

#### Case Report:

A rare case of permanent neonatal diabetes mellitus presented with intrauterine growth retardation (IUGR; birth weight: 1460 grams; female), hyperglycemia, glycosuria, and mild dehydration, a normal Apgar score of 8 and 9 at 1 and 5 minutes, respectively. The parents, of consanguineous union, had no prior history of diabetes mellitus. Of their 4 children, the first child had a diagnosis similar to the patient (their last child). The patient was initially started on continuous infusion of insulin, and then switched to regular insulin subcutaneously, but response was sub-optimal. She was started on neutral protamine Hagedorn, following which her condition improved. She was discharged on neutral protamine Hagedorn with regular follow-up.

#### Conclusions:

In view of widespread consanguinity in Saudi Arabia it appears prudent and pertinent to suspect permanent neonatal diabetes mellitus following diagnosis of hyperglycemia in small-for-age infants, especially those with positive family history of diabetes. Close blood glucose monitoring is essential as long as hyperglycemia persists. Prolong follow-up is imperative.

#### key words:

**consanguinity • diabetes • hyperglycemia • insulin • neonatal • neutral protamine Hagedorn**

#### Full-text PDF:

<http://www.amjcaserep.com/fulltxt.php?ICID=883242>

#### Word count:

965

#### Tables:

–

#### Figures:

–

#### References:

13

#### Author's address:

Abdulrahman Al-Matary, Department of Neonatology, Children's Hospital, King Fahad Medical City King Fahad Medical City, Riyadh, Saudi Arabia, P.O Box 59046, Riyadh Email: aalmatary@kfmc.med.sa

## BACKGRIUND

Neonatal diabetes is a rare cause of hyperglycemia. The incidence of this condition is estimated to be approximately 1 in 500,000 births [1]. Neonatal diabetes mellitus is defined as persistent hyperglycemia occurring in the first months of life, which lasts more than 2 weeks, and which requires insulin for management. The infants are usually small for gestational age. This may be related to decreased insulin secretion in the fetus. Affected infants usually present with weight loss, volume depletion, hyperglycemia, and glucosuria with or without ketonuria and ketoacidosis [2]. If hyperglycemia is persistent in infants younger than 6 months (plasma glucose concentration >150–200 mg/dl), the condition would be compatible with the diagnosis of permanent neonatal diabetes mellitus (PNDM) [3,4]. Clinical manifestation of PNDM at the time of diagnosis would be consistent with the following findings: intrauterine growth retardation (IUGR), hyperglycemia, glycosuria, osmotic polyuria, dehydration and failure to thrive (FTT). Therapy with insulin ameliorates the hyperglycemia and promotes catch-up growth [3,4].

## CASE REPORT

This female neonate was born at 36 weeks of gestation through normal spontaneous vaginal delivery to parents of a consanguineous union. The mother was 25 years old, with an obstetric history of gravida 4 and para 4. She had attended regular antenatal check-ups. This pregnancy was complicated by IUGR and preterm delivery. Birth weight was 1460 grams (<3<sup>rd</sup> centile). Physical examination of the infant was normal. Apgar score was 8 and 9 at 1 and 5 minutes, respectively, and no resuscitation was required at birth. She was admitted into the high dependency unit (HDU) at 1 hour of age due to low birth weight and IUGR. No history of gestational diabetes or any drug use during pregnancy was noted.

On examination she was tachypneic, lethargic and mildly dehydrated, with no dysmorphic facies. She was started on dextrose water 10% but was soon switched to dextrose water 7.5% and dextrose water 5% due to persistent hyperglycemia. When serum glucose was >200 mg/dl she was started on neonatal hyperglycemia protocol.

Laboratory investigations demonstrated hyperglycemia (210 mg/dl), metabolic acidosis, C-peptide level: 0.102 nmol/l (low), serum insulin level: 3.7 pmol/l (low), normal urea and electrolytes. The problem was resolved with appropriate therapy and persistent hyperglycemia was treated with continuous intravenous (0.1–0.7 U/kg/h) and subsequent subcutaneous insulin therapy. Neutral protamine Hagedorn (NPH) insulin was started on the 10<sup>th</sup> day of life due to blunt response of regular subcutaneous insulin. She was discharged on twice daily NPH insulin regimen. The family was educated and trained on insulin dosing, and management of hyperglycemia and hypoglycemia. Subsequent follow-up was undertaken in the Department of Neonatology and Endocrinology Clinic.

## DISCUSSION

The definition of hyperglycemia is uncertain. It is often defined as blood glucose >125 mg/dL (6.9 mmol/L) or plasma

glucose >150 mg/dL (8.3 mmol/L). These glucose levels are frequently observed during glucose infusions in newborns, especially in extremely preterm infants, and may not require intervention [5]. The course of neonatal diabetes is variable. About one-half of patients with neonatal diabetes mellitus have a permanent form that is primarily due to gene mutations related to the ATP-sensitive potassium channel [6]. KCNJ11 gene encoding Kir6.2, the most common cause of permanent neonatal diabetes, is due to activating mutations in the KCNJ11 gene, which encodes Kir6.2 [5,6]. The diagnosis is made within the first 2 months of life [7]. Small-for-gestational age infants exhibit postnatal catch-up growth with insulin therapy [8]. Affected patients can have neurological abnormalities, including severe developmental delay, epilepsy, muscle weakness, and dysmorphic features. These findings are also known as the DEND syndrome (developmental delay, epilepsy, neonatal diabetes) [3]. Subcutaneous insulin was routinely used in the past to treat patients with this disorder; however, oral sulfonylurea therapy appears to be more effective in controlling hyperglycemia [9]. Interventions to reduce the blood glucose concentration are initiated at values above 180 to 200 mg/dL (10 to 11.1 mmol/L). The first step in management is to decrease the glucose infusion rate. Reducing the rate to 4 to 6 mg/kg per minute usually lowers the blood glucose concentration. In most cases, this is accomplished by reducing the concentration of the dextrose solution from 10% to 5%. If provided with parenteral nutrition solution and lipid emulsion, infants can maintain normoglycemia with the reduced glucose supply by gluconeogenesis from glycerol and amino acids [10]. Insulin improves glucose tolerance, allows provision of more calories, and promotes growth in infants who remain hyperglycemic at reduced glucose infusion rates [11].

Insulin infusion should be considered in infants with persistent hyperglycemia (>200 to 250 mg/dL [11.1 to 13.9 mmol/L]) despite reductions in glucose infusion rate and in those who fail to thrive because of reduced caloric intake [12]. Regular insulin in 5% dextrose solution should be infused at an initial dose of 0.01 units/kg per hour after priming the infusion tubing with the insulin solution. Blood glucose concentration should be monitored frequently and the dose of insulin adjusted in small increments up to 0.1 units/kg per hour to maintain glucose levels of 150 to 200 mg/dL (8.3 to 11 mmol/L). The insulin infusion should be tapered and discontinued as soon as glucose tolerance improves [11,12].

The present case of PNDM may be attributed to consanguinity, which is well documented to be in the order of about 58% in Saudi Arabia [13] and is believed to be as high as above 80% in isolated Saudi Arabian communities [13]. There is increasing evidence that consanguinity is contributing to a vast array of disease states in populations practicing marriage among close relatives.

## CONCLUSIONS

In view of widespread consanguinity in Saudi Arabia and neighboring countries, it appears prudent and pertinent to suspect permanent neonatal diabetes mellitus when hyperglycemia is diagnosed alongside small-for-age infants, especially, with positive family history of diabetes. Close blood glucose monitoring is essential as long as hyperglycemia persists. Prolonged follow-up is imperative.

---

**REFERENCES:**

---

1. Von Muhlen Dahl KE, Herkenhoff H: Long-term course of neonatal diabetes. *N Engl J Med*, 1995; 333: 704–8
2. Kalhan SC, Parimi PS: Disorders of carbohydrate metabolism. In: *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*, 7<sup>th</sup> ed, Fanaroff AA, Martin RJ (eds.). Mosby, St. Louis. 2002. P.1351
3. Hattersley AT, Ashcroft FM: Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. *Diabetes*, 2005; 54: 2503–13
4. Porter JR, Shaws NJ, Barrett TG, Hattersley AT: Permanent neonatal diabetes in an Asian infant. *J Pediatr*, 2005; 146: 131–33
5. Louik C, Mitchell AA, Epstein MF, Shapiro S: Risk factors for neonatal hyperglycemia associated with 10% dextrose infusion. *Am J Dis Child*, 1985; 139: 783
6. Chen R, Hussain K, Al-Ali M et al: Neonatal and late-onset diabetes mellitus caused by failure of pancreatic development: report of 4 more cases and a review of the literature. *Pediatrics*, 2008; 121: e1541
7. Gloyn AL, Pearson ER, Antcliff JF et al: Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med*, 2004; 350: 1838
8. Slingerland AS, Hattersley AT: Activating mutations in the gene encoding Kir6.2 alter fetal and postnatal growth and also cause neonatal diabetes. *J Clin Endocrinol Metab*, 2006; 91: 2782
9. Pearson ER, Flechtner I, Njolstad PR et al: Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*, 2006; 355: 467
10. Sunehag AL, Haymond MW, Schanler RJ, Reeds PJ: Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. *Diabetes*, 1999; 48: 791
11. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL et al: Early insulin therapy in very-low-birth-weight infants. *N Engl J Med*, 2008; 359: 1873
12. Vaucher YE, Watson PD, Morrow G III: Continuous insulin infusion in hyperglycemic, very low birth weight infants. *J Pediatr Gastroenterol Nutr*, 1982; 1: 211
13. el-Hazmi MA, al-Swailem AR, Warsy AS et al: Consanguinity among the Saudi Arabian population. *J Med Genet*, 1995; 32(8): 623–26