NEONATAL DIABETES MELLITUS IN 2,5 MONTH OLD CHILDREN

Ivanny Khosasih[1*], Eka Agustia Rini
Department of Pediatrics, Endocrinolgy Division, Faculty of Medicine, Andalas University,Dr. M. Djamil Hospital, Padang, West Sumatera, Indonesia
*Email Korespondensi: vanny_doct06@yahoo.com

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ABSTRACT

Neonatal Diabetes mellitus (NDM) is a rare genetic disease (1 in 90,000 live births). It is defined by the presence of severe hyperglycaemia associated with insufficient or no circulating insulin, occurring mainly before 6 months of age and rarely between 6 months and 1 year. Such hyperglycaemia requires either transient treatment with insulin in about half of cases, or permanent insulin treatment. In transient NDM, growth-retarded infants develop diabetes in the first few weeks of life, only to go into remission after a few months with possible relapse to permanent diabetes usually around adolescence or in adulthood. In permanent NDM, insulin secretory failure occurs in the late fetal or early postnatal period. We present a case of 9 months old boy with neonatal diabetes mellitus since 2 months 15 days old. He had history of fever, polyuria, polydypsia, tachypnoe and diabetic ketoacidosis. He came with hyperglycemia, positive urine ketone and acidosis. C-peptide result was low (0,1 mg/dl). Patient was hospitalized for acute conditions according to DKA management and continued with insulin subcutaneous. Neonatal diabetes mellitus was a rare condition. The cardinal symptoms of NDM include hyperglycemia at birth, IUGR, failure to thrive, dehydration, and, rarely, ketoacidosis. Treatment with insulin should be started immediately after diabetes is diagnosed by persistent hyperglycemia or elevated glycated hemoglobin (HbA1c). The prognosis is related to the severity of the disease, the degree of dehydration and acidosis, as well the rapidity with which the disease is recognized and treated. Prognosis also depends on metabolic control.

Keywords: *neonatal, hyperglycemia, diabetes mellitus.*

ABSTRAK

Neonatal Diabetes mellitus (NDM) adalah penyakit genetik langka (1 dari 90.000 kelahiran hidup). Ini didefinisikan oleh adanya hiperglikemia berat yang berhubungan dengan insulin yang tidak mencukupi atau tidak ada sirkulasi, terjadi terutama sebelum usia 6 bulan dan jarang antara 6 bulan dan 1 tahun. Hiperglikemia seperti itu memerlukan pengobatan sementara dengan insulin pada sekitar setengah kasus, atau pengobatan insulin permanen. Pada NDM transien, bayi dengan retardasi pertumbuhan mengembangkan diabetes dalam beberapa minggu pertama kehidupan, hanya untuk mengalami remisi setelah beberapa bulan dengan kemungkinan kambuh menjadi diabetes permanen biasanya sekitar masa remaja atau dewasa. Pada NDM permanen, kegagalan sekresi insulin terjadi pada akhir periode janin atau awal pascanatal. Kami menyajikan kasus anak laki-laki berusia 9 bulan dengan diabetes mellitus neonatal sejak 2 bulan 15 hari. Dia memiliki riwayat demam, poliuria, polidipsia, takipnea dan ketoasidosis diabetikum. Dia datang dengan hiperglikemia, keton urin positif dan asidosis. Hasil C-peptida rendah (0,1 mg/dl). Pasien dirawat inap karena kondisi akut sesuai penatalaksanaan DKA dan dilanjutkan dengan insulin subkutan. Diabetes mellitus neonatus adalah kondisi yang jarang terjadi. Gejala utama NDM termasuk hiperglikemia saat lahir, IUGR, gagal tumbuh, dehidrasi, dan, jarang, ketoasidosis. Pengobatan dengan insulin harus dimulai segera setelah diabetes didiagnosis dengan hiperglikemia persisten atau peningkatan hemoglobin terglikasi (HbA1c). Prognosis berhubungan dengan keparahan penyakit, derajat dehidrasi dan asidosis, serta kecepatan penyakit dikenali dan diobati. Prognosis juga tergantung pada kontrol metabolik.

Kata kunci: *neonatus, hiperglikemia, diabetes mellitus.*

BACKGROUND

Diabetes mellitus (DM) is a heterogeneous group of metabolic diseases and can present at any age, from birth to old. Neonatal diabetes mellitus (NDM) is considered as a rare disorder, but probably underestimated. It can be transient (TNDM) or permanent (PNDM) which develop within the first few weeks or months of life, with an incidence of 1 in 300,000 to 500,000 live births . [1,2] The genetic causes of NDM have been identified in 90% of TNDM and 70% of PNDM cases.[3]

NDM is predominantly monogenic in origin. Approximately 70% of TDNM cases are caused by abnormalities in chromosome 6q24, and 25% by mutations of the K channel genes *KCNJ11* and *ABCC8*. The most common causes of PNDM include mutations of *KCNJ11* (approximately 30–50% of cases), *ABCC8* (9–10%), and *INS* (12–20%). Most infants with NDM require insulin to improve their metabolic abnormalities and facilitate weight gain. Patients with activating mutations of the K ATP channel genes can usually be transitioned to a sulfonylurea after initial insulin treatment.[4]

Transient neonatal diabetes mellitus (TNDM) occurs in 60% of all NDM cases. This patient requires initial insulin administration recovery is expected to occur spontaneously after 12 weeks. Nonetheless, more than 50% of cases of TNDM relapse and develop into type 2 diabetes mellitus in adolescence. Permanent neonatal diabetes mellitus (PNDM), the other type of NDM, is rare. In all forms of NDM found insulinopenia is found due to abnormal development of pancreatic islet cells, decreased pancreatic β cell mass, or β cell dysfunction.[5] There is no clinical features that can predict neonates with diabetes (without other dysmorphic images) will eventually become permanent NDM or transient NDM. Recent research shows that molecular mechanism of pancreatic development is related to PNDM and TNDM.[6]

Neonatal diabetes mellitus is a condition that remains a challenge for clinicians both in terms of diagnosis and treatment due to the variety of possible etiologies of NDM, as well as the physiology of infants in the face of hyperglycemia, and even threatening complications. The aim of this presentation is to highlight the distinctive manifestation, diagnosis and management of neonatal diabetes mellitus.

CASE REPORT

A 9 months old boy, was hospitalized in the pediatric ward of Dr M. Djamil Padang Hospital for 25 days. He have been diagnosed with diabetes mellitus since the age of 2 months 15 days by pediatrician, he got novomix 2 units / day and novorapid if blood sugar > 180 mg / dl. His blood sugar range 50 - 380 from the age of 2 months 15 days. He had fever 15 days ago, and now none of fever. None of another complains. Urinate and defecation was within normal limit. He get breastfed on demand until now and get milk porridge in 6 months, because his blood glucose was always high sometimes the porridge was stopped.

Patient had 3 times hospitalized, the first hospitalization because unconsiousness with hyperglycemia, the second and the third because fever, seizure and hypoglycemia. There is no family history of suffering diabetes mellitus. There is no history of consanguinity in family. Patient was the second child. He was born with caesarean delivery by obstetrician due to prolong labour and unsuccessful induction, aterm, body weight 2.800 gram, body lenght 49 cm, immediately cried. Patient had not got any immunization from birth. Growth were normal and development were delayed. The patient can't raised head. Patient and his family live in a permanent house with hygiene and sanitation was not good.

On the physical examination**,** the general condition of the child appeared to be moderately ill, alert. His pulse rate of

18 beats / minute, respiratory rate of 22 times / minute, and body temperature of 38^0C. He did not look pale, icteric, nor cyanotic. His length was 62 cm and body weight was 7,5 kg, well-nourished child. Skin was warm, skin elasticity return quickly. Head circumference was 45 cm (normocephalic). No palpebral oedema, There was phymosis. There is no abnormality on another physical examination.

Complete blood count tests showed haemoglobin of 10,6 g / dl, leukocytes of 22,890/mm^3, hematocrit of 29%, platelets of 411,000 / mm3, sodium 135 mmol/lt, potassium 4,7 mmol/lt, calsium 10,3 mg/dl, RBG 502 mg/dl, ureum 11 mg/dl, creatinin 0,2 mg/dl. Blood gas analysis : pH 7,32 / pCO2 34 / pO2 27 / HCO3- 17,4 / BE 7,6 / SO2 42%. Urine: colour light yellow, pH 1,005, leucocyte 0 – 1, erithrocyte 0 – 1, glucose ++, protein -, keton ++. C peptide 0,1 mg/dl, HbA1C 11,2%

The working diagnosis were ketoacidosis diabeticum due to neonatal diabetes mellitus, phimosis and delayed motoric. He got treatment according to DKA treatment (water resuscitation and insulin drip). Blood glucose were checked every hours and urine ketone was checked every 2 hours. Random blood glucose was in range 50-399mg/dl. Because the blood glucose was stable and urine ketone negative, the treatment change to insulin subcutaneous and get glibenclamide 0,1mg/kgbw/day. He was discharge after 25 days hospitalization and followed outpatient. 3 month after followed his blood glucose range was 100-250 mg/dl and control by insulin subcutaneous. In 1 years, he can sit and 1 years 6 month he can walking. The patient planned to DNA analysis.

DISCUSSION

We present a case of a 9 months old boy with known neonatal diabetes melitus since 2 months 15 days old. He had history of fever, unconsciousness and seizures due to the instable of the blood glucose. Sepsis, surgical procedure, anesthesia, and other critical illnesses can lead to elevation of blood sugar levels, potentially secondary to a stress response and concomitant rise in epinephrine and cortisol, decreased insulin release, and impaired glucose utilization.[7] NDM should be considered in infants with insulin-dependent hyperglycemia, with glucoses persistently greater than 250mg/dl, without an alternative cause. Clinicians should become suspicious of diabetes when hyperglycemia persists for longer than 7 to 10 days.[8]

In monitoring, random blood glucose reaches a high level, positive urine ketone and acidosis. Ketoacidosis can occur inneonatal diabetes mellitus patients. Neonates and infants presenting with diabetic ketoacidosis should be managed in an intensive care unit, under the supervision of a pediatric endocrinologist. Patient was treated for acute conditions according to DKA management. The main initial management includes fluid rescusitation with isotonic electrolyte solutions, to treat dehydration that results from osmotic diuresis, frequent monitoring of blood glucose, electrolytes, and neurological status.[9]

Neonatal diabetic ketoacidosis is managed according to the same principles guiding the therapy for children and adolescents with diabetes mellitus.[10] Insulin therapy should be started with careful attention as newborns are very sensitive to insulin and therefore in danger of severe hypoglycemia. A continuous intravenous infusion of regular insulin is started at 0.05-0.1 U/kg/hr and titrated up or down as needed based on the blood glucose levels. The goal of therapy is to allow normal energy utilization by tissues as well as to replace fluids and electrolytes.[9] After the initial treatment of the diabetic ketoacidosis, the intravenous infusion of regular insulin should be continued in infants with persistent hyperglycemia, despite reductions in glucose infusion rates, and in those with

persistent glucose excursions, while others are transitioned to an appropriate regimen of subcutaneous insulin.[11]

However, the patient returned to severe hyperglycemia and followed by periods of hypoglycemia. Child with NDM are susceptible to hypoglycemia because of the relatively low insulin requirements. Insulin therapy is crucial in neonatal DM to obtain satisfactory weight gain and growth in these infants. A variety of methods for providing insulin such as: intravenous infusion, short−acting and long−acting subcutaneous injections, or continuous subcutaneous insulin infusion (CSII) can be used. [12] In a study by Mitamura et al, control of the blood glucose concentration in infants with TNDM was attained with ultralente insulin treatment without any episodes of hypoglycaemia.[13] In some centres in Europe, the use of CSII in all cases of neonatal DM is proposed, stating that during the neonatal period, CSII therapy is safe, more physiological, more accurate and easier to manage than injections.[14] Continous subcutaneous insulin infusions (CSII) allow for very small accurate doses to be given in a physiologic way, with a continuous basal dose (as low as 0.025 units/hr) that may be adjusted hourly.

Unfortunately, this device is not available in our country. In our case, blood glucose levels were successfully controlled with insulin basal bolus treatment, and no serious complications have been observed. Patient had given basal and bolus subcutaneous insulin dissolved in 0.9% NaCl. Random blood glucose ranges from 50-380 mg/dl but he still experience periods of hypoglycemia and hyperglycemia.

Of the known genetic subtypes of NDM, only patients with activating *KCNJ11* or *ABCC8* gene mutations respond to treatment with a sulfonylurea. TNDM subtype with 6q24 methylation disorders can also be treated with low-dose sulfonylurea.[15] To switch treatment rapidly in hospital inpatients, glyburide was started at a dose of 0.1 mg per kilogram twice daily and was increased daily by 0.2 mg per kilogram per day. To switch treatment more slowly in outpatients, glyburide was introduced at a dose of 0.1 mg per kilogram per day and was increased by 0.1 mg per kilogram per day once a week. The dose of glyburide was increased until insulin independence was achieved or the dose was at least 0.8 mg per kilogram per day.[16] Our patient had got glibenclamid 0,1mg/kgbw/day but there was no significance effects. The sulfonylurea is then stopped and subcutaneous insulin continous.

Sulfonylurea can be started in a patient as soon as the genetic diagnosis is established, and a trial of sulfonylurea in NDM without a genetic diagnosis is not recommended.[17] However, some studies show that Sulfonyurea can also be given in conjunction with insulin to observed the therapeutic response before the results of genetic testing come out. Management of NDM without genetic examination is monogenic with therapeutic tailoring, because the response of each individual is different, diverse types with diverse pathophysiology as well.[15]

The etiology of NDM is unclear and its pathogenesis differs from insulin−dependent childhood DM. Presence of islet cell antibodies has not been reported in NDM. [18] A number of syndromic and genetic constellations, such as Wolcott−Rallison syndrome (autosomal recessive), immune dysregulation, polyendocrinopathy, enteropathy, X−linked (IPEX) syndrome (X−linked, recessive), phosphoribosyl−ATP pyrophosphate hyperactivity (X−linked), and glucokinase deficiency (MODY2) have been reported in PNDM.[2,12]

Wolcott−Rallison syndrome is characterized by the appearance of PNDM within the first few weeks of life. It is also related with multiple epiphyseal or spondylo−epiphyseal dysplasia, cardiac anomaly, recurrent hepatitis, and ectodermal dysplasia. [1,12,19] In our patient, there were no signs of the above−mentioned abnormalities.

This patient was born aterm and normal body weight, there were development disorders, no spesific clinical features related syndromes. No familial hystory of diabetes. There was no symptoms of immune dysfunctions. IUGR is often found in TNDM patients, typically developing in the third trimester, such that the birth weight is typically 1.5-2.5 kg.[20] Low birth weight can be regarded as a bioassay for in utero insulin secretion since insulin's role as growth factor is an important component of fetal growth. The incidence of neonatal macrosomia in the setting of uncontrolled maternal diabetes or gestational diabetes is further evidence for insulin-mediated growth. It is important to note that maternal insulin cannot cross the placental barrier, and therefore, the failure of the developing fetus to produce insulin severely affects fetal growth parameters, including weight, length, and head circumference. The TNDM patients were diagnosed at an earlier age (median age 6 days; range 1-81 days) relative to the PNDM patients (median age 27 days; range 1-127 days). The birth weight was also significantly lower in the TNDM patients (1,987±510 g) compared with the PNDM patients (2,497±610 g). Although the reasons are not clear, it is hypothesized that a defect in B-cell function and/or development is present in early postnatal life in TNDM, while satisfactory fetal B-cell function and/or development followed by a rapid B-cell failure after birth occurs in PNDM.[21]

Genetic examination was planned to checked in outpatient clinic, the test still pending because of high cost and should be sent to Exeter medical school NHS foundation England research. Approximately 39% of PNDM cases and about 11% of maturity onset diabetes of the young (MODY) have an unknown genetic aetiology.[22]

The patient had been hospitalized for 25 days and discharged with stable conditions. Random blood glucose range from 100-250mg /dl with insulin basal bolus. The most important of the management of diabetes mellitus is education. The family was educated how to check random blood glucose, administration and dilution of insulin, signs of hypoglycemia or hyperglycemia and the management of emergency conditions.

In the last control, the patient was stable with subcutaneous basal insulin at a dose of 5 IU / day (0.4IU/kg/day). TNDM usually show improvement before the age of 18 months, but there were also found TNDM patients with insulin dependent until the age of 8 years.[21,23] In this patient a dose reduction was tried but the random blood glucose was still stable at 0.4 IU/day of basal bolus insulin dose.

Prognosis of patients with NDM depends on metabolic control, severity of the disease and existance of conditions such as dehydration or acidosis. Worse prognosis in NDM related syndrome, it could be growth disorders, neurodevelopment and even death. On 12 months observation, the patient is still in stable condition, the increase in body weight is suitable with growth and development charts according to age. Random blood glucose was stable in range of 80-280 mg/dl.

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