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Neonatal diabetes mellitus in developing country: A rare case report

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Abstract: Neonatal Diabetes Mellitus (NDM) is a rare monogenic form of diabetes characterized by persistent hyperglycemia within the first six months of life. Managing NDM presents significant challenges due to variations in insulin sensitivity and glycemic fluctuations. This report aims to elucidate the diagnostic difficulties and therapeutic strategies in resource-limited settings. A two-month-old male infant presented with respiratory distress, fever, and productive cough, accompanied by Kussmaul respiration. Laboratory investigations revealed a random blood glucose level of 637 mg/dL, +3 urine ketones, and an HbA1c of 9.4%, consistent with diabetic ketoacidosis (DKA). Considering his age and clinical presentation, NDM was suspected. Continuous intravenous insulin infusion resulted in marked glycemic fluctuations, with glucose levels ranging from less than 100 mg/dL to 550 mg/dL. A C-peptide stimulation test performed after administering glibenclamide showed an increase from 0.7 to 2.2 ng/mL, indicating preserved β-cell function. Respiratory distress combined with persistent hyperglycemia in infants may suggest DKA. Transitioning from insulin to sulfonylurea therapy, guided by C-peptide testing, highlights the importance of early diagnosis of NDM and personalized treatment approaches to optimize metabolic control. Early recognition of NDM in infants with persistent hyperglycemia and appropriate sulfonylurea therapy can simplify management and improve long-term outcomes, especially in resource-limited settings.

Keywords: *C-peptide stimulation test, Hyperglycemia, Insulin therapy, Neonatal diabetes mellitus.*

1. Introduction

Neonatal Diabetes Mellitus (NDM) is a rare monogenic form of diabetes characterized by the onset of persistent hyperglycemia, typically occurring within the first six months of life, although it can present up to the age of one year. Affecting approximately 1 in 90,000-160,000 live births, NDM is primarily caused by a genetic mutation in one of over 20 identified genes that are crucial for the development and function of pancreatic beta-cells. Unlike type 1 diabetes, NDM is not an autoimmune condition. NDM results from single-gene mutations affecting insulin secretion. It can be classified as Transient Neonatal Diabetes Mellitus (TNDM), where the condition resolves, usually within the first year, or Permanent Neonatal Diabetes Mellitus (PNDM), which requires lifelong management. The underlying pathophysiology involves either a malformation of the pancreas or an abnormal function of existing beta-cells, leading to insufficient insulin secretion [1, 2].

The clinical presentation of NDM can range from asymptomatic hyperglycemia to severe diabetic ketoacidosis (DKA), making early diagnosis a critical challenge. The initial symptoms often include polyuria, polydipsia, and failure to thrive, which can be mistaken for other common neonatal issues. This

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diagnostic complexity underscores the importance of prompt identification and intervention to prevent severe complications. Furthermore, a significant number of patients with TNDM, up to 86%, experience a relapse of diabetes during puberty, reinforcing the need for close and prolonged follow-up by a multidisciplinary pediatric team. Management is further complicated by the high sensitivity of neonates to insulin and the need for precise glycemic control to avoid both hyperglycemia and the detrimental cognitive effects of hypoglycemia [1, 3].

Given its rarity, NDM has been studied relatively infrequently, and clear, evidence-based recommendations for optimal management are still evolving. Genetic testing has emerged as a cornerstone of diagnosis, as identifying the specific mutation can fundamentally alter the treatment approach, such as enabling a successful transition from insulin to oral sulfonylureas in patients with KCNJ11 or ABCC8 mutations. This personalized medicine approach has been shown to improve not only glycemic control but also neurodevelopmental outcomes. Therefore, this report aims to present a rare case of neonatal diabetes mellitus, with a specific focus on the diagnostic process, the challenges of initial management with insulin therapy, and the subsequent transition to oral medication based on clinical and laboratory responses [1, 4, 5].

2. Case Presentation

A two-month-old Javanese male infant, identified as I.F., was referred from a regional general hospital and presented to the emergency department of Dr. Soetomo Hospital on December 31, 2022, with the chief complaint of shortness of breath. The symptoms had been present for two days prior to admission and were accompanied by fever, a productive cough, and vomiting. The parents also noted that the infant seemed excessively thirsty, was consuming more milk than usual, and had frequent urination. Additionally, he exhibited general weakness. There were no reports of edema, headache, diarrhea, or seizures.

The patient had a significant prior medical history of being admitted to Tuban General Hospital at one month of age for fever and shortness of breath, where he was found to have a blood sugar level up to 500 mg/dL. He received intravenous insulin therapy during that admission before being referred. He was born at full term via cesarean section due to fetal bradycardia, with a birth weight of 2900 grams and a length of 51 cm. His growth and development were appropriate for his age, and he had completed all basic immunizations as scheduled. There was no family history of diabetes mellitus or other endocrine disorders. His parents were healthy and had a good history of antenatal care.

Upon physical examination at Dr. Soetomo Hospital, the patient's vital signs were a heart rate of 150-158 beats per minute, a respiratory rate of 40-55 breaths per minute, and a temperature of 38.5-38.8°C. His blood pressure was 80/50 mmHg. He showed signs of dehydration, including sunken eyes and slow skin turgor, with clammy extremities. His breathing was vesicular with no retractions, rhonchi, or wheezing noted. The abdomen was supple with normal bowel sounds. Anthropometric measurements showed a weight of 4.4 kg and a length of 56 cm, which plotted between 0 and -2 SD on the WHO growth charts for weight-for-age, length-for-age, and weight-for-length, indicating a normoweight status.

Initial laboratory investigations from the referring hospital revealed a hemoglobin of 9.6 g/dL, a random blood glucose of 637 mg/dL, hyponatremia with sodium at 127 mmol/L, a pH of 7.32, and +3 urine ketones. At Dr. Soetomo Hospital, his blood glucose was 439 mg/dL, with a serum ketone level of 2.4 mmol/L and an HbA1c of 9.4%. These collective findings of persistent, severe hyperglycemia with ketosis and classic diabetic symptoms in an infant under six months old, supported by history and physical examination, confirmed the diagnosis of Neonatal Diabetes Mellitus (NDM).

The patient's management began immediately in the emergency room with rehydration and continuous intravenous insulin therapy via an insulin pump, initiated at a rate of 0.05 units/kg/hour (2.2 ml/hour). Despite this, his blood glucose initially rose to 550 mg/dL with ketones at 4.6 mmol/L within two hours. Over the next several hours, with adjustments to the insulin rate, his glucose level dropped, at one point falling below 100 mg/dL, which prompted a temporary cessation of the insulin

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pump. However, hyperglycemia quickly recurred, necessitating the resumption of the insulin pump at a lower rate. The therapeutic goal was to maintain blood glucose levels between 150-250 mg/dL through regular monitoring and insulin rate adjustments.

During hospitalization, the patient's blood glucose profile demonstrated considerable variability. On the first day, glucose levels ranged from 439 mg/dL to as high as 550 mg/dL, with ketone levels up to 4.6 mmol/L, before dropping below 100 mg/dL, which required temporary cessation of insulin infusion. Over the following two to four days, blood glucose remained unstable, fluctuating widely between hypoglycemia (<100 mg/dL) and severe hyperglycemia (400 mg/dL) despite frequent adjustments of insulin dosage. By the fifth day, relative stabilization was achieved after the initiation and titration of oral glibenclamide. On days six to eight, glucose levels tended to improve, although a subsequent rise was observed on day eight, prompting the addition of basal insulin analog (Levemir). From days nine to eleven, the combination therapy with glibenclamide and basal insulin successfully maintained glucose levels within the target range, without episodes of severe hypoglycemia.

To guide further therapy, a C-peptide test was performed, which showed a baseline level of 0.7, indicating low endogenous insulin production. After a trial of glibenclamide, the C-peptide level increased to 2.2, demonstrating a positive response to sulfonylurea (SU) stimulation. Following relatively stable blood glucose levels on the third day of admission, oral glibenclamide was started at a dose of 0.6 mg/kg/day, and the insulin pump was gradually tapered off, being completely stopped on the fifth day. Due to a subsequent elevation in blood glucose on the eighth day, basal analog insulin (Levemir) was added to the regimen. With the combination of glibenclamide and Levemir, the patient's blood sugar levels stabilized within the target range, and he was discharged on the 12th day of admission.

3. Discussion

This report details the case of a two-month-old infant presenting with respiratory distress who was subsequently diagnosed with Neonatal Diabetes Mellitus (NDM). The patient exhibited the classic triad of diabetic symptoms, including polydipsia, polyuria, and significant hyperglycemia, which progressed to a state of diabetic ketoacidosis (DKA). The presentation of NDM can vary from incidental asymptomatic hyperglycemia to severe DKA, and this case highlights a more severe manifestation that necessitated immediate and intensive intervention. The diagnosis was established based on the patient's age and persistent hyperglycemia, aligning with the defining characteristics of NDM [6].

The initial chief complaint of shortness of breath is a common symptom in ambulatory pediatrics with a broad differential diagnosis. In this case, the dyspnea was a direct consequence of the underlying severe metabolic acidosis, a compensatory mechanism known as Kussmaul breathing. This underscores a critical clinical lesson: in an infant presenting with respiratory distress and signs of dehydration, a metabolic cause such as diabetic ketoacidosis (DKA) must be considered early in the diagnostic process. The presence of persistent hyperglycemia for longer than seven to ten days in a neonate, especially when accompanied by glucosuria and ketonuria, should strongly raise suspicion for neonatal diabetes mellitus (NDM) over more common causes of transient neonatal hyperglycemia [6, 7].

A crucial diagnostic step in any infant with diabetes is differentiating NDM from autoimmune Type 1 Diabetes (T1D). The patient's age of onset under six months is the most significant factor pointing away from T1D, which is exceedingly rare in this age group. NDM is a monogenic disorder resulting from specific gene mutations affecting beta-cell function, not an autoimmune process. Therefore, the plan to proceed with genetic testing for this patient is consistent with the current best practice guidelines. A definitive genetic diagnosis is vital as it not only confirms the etiology but can fundamentally guide therapeutic decisions, moving beyond conventional insulin therapy toward precision medicine [6, 8].

The initial management of this patient with a continuous subcutaneous insulin infusion (CSII) or insulin pump highlights the considerable challenges of glycemic control in this population. Neonates are exquisitely sensitive to insulin, leading to significant glycemic variability, as demonstrated in this case,

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where blood glucose levels fluctuated between severe hyperglycemia (>500 mg/dL) and hypoglycemia (<100 mg/dL) despite frequent insulin rate adjustments. While CSII is a recommended strategy to provide more physiologic insulin delivery and mitigate this volatility, this case illustrates that achieving stable glucose levels remains difficult. This reinforces the need for management in a specialized center with expertise in neonatal diabetes [9].

The decision to trial sulfonylurea (SU) therapy was based on an understanding of the underlying pathophysiology of the most common forms of permanent neonatal diabetes mellitus (NDM). Mutations in the *KCNJ11* and *ABCC8* genes, which encode the Kir6.2 and SUR1 subunits of the pancreatic ATP-sensitive potassium (KATP) channel, are the leading cause of permanent neonatal diabetes mellitus (PNDM). These activating mutations prevent the channel from closing in response to ATP, thereby inhibiting glucose-stimulated insulin secretion. Sulfonylureas act by binding directly to the SUR1 subunit, forcing the KATP channel to close, which restores the beta-cell's ability to secrete endogenous insulin in response to glucose [10, 11].

This case serves as a prime example of implementing precision medicine in practice. The use of a C-peptide test before and after a glibenclamide challenge was a pivotal investigation. The significant rise in C-peptide from 0.7 to 2.2 after the challenge strongly predicted that the patient's beta-cells were viable and responsive to SU therapy. This functional test provided the confidence to transition the patient from the burdensome regimen of CSII to oral glibenclamide. The successful switch, which allowed for the complete discontinuation of the insulin pump, dramatically simplified the treatment regimen and directly aligned with modern management paradigms informed by genetic and pathophysiological insights [11, 12].

The long-term efficacy and safety of SU therapy in NDM due to KATP channel mutations are well-established. A 10-year international cohort study demonstrated that patients maintain excellent glycemic control, with a mean HbA1c of 6.4%, on long-term SU treatment. Importantly, this is achieved without a significant risk of severe hypoglycemia, a major concern with insulin therapy. Furthermore, early initiation of SU therapy has been associated with improvements in neurodevelopmental outcomes, as the drugs can cross the blood-brain barrier to act on similar KATP channels in the central nervous system. This case, therefore, highlights a therapeutic choice with proven long-term benefits for both metabolic control and neurological function [10-12].

Despite the remarkable success of SU therapy, this case also illustrates that it may not be a panacea for all patients. The latter needs to add basal analog insulin (Levemir) to the patient's regimen to maintain target glucose levels, demonstrating that combination therapy is sometimes necessary. Insulin detemir's mechanism of action, involving reversible binding to albumin, provides a prolonged and relatively peakless profile, making it a suitable adjunct to SU therapy. It can provide a stable basal insulin level to cover periods between meals, complementing the meal-stimulated insulin release triggered by sulfonylurea, thereby optimizing overall glycemic control.

Long-term management for any child with NDM requires a dedicated, multidisciplinary team approach. Regular follow-up, at least every three months in infancy, is essential to monitor growth, glycemic control (via HbA1c after 6 months of age), and adjust therapy as needed. Given that even transient forms of NDM have a very high rate of relapse into permanent diabetes during puberty, lifelong surveillance is imperative. Families must be educated on recognizing the subtle signs of hypoglycemia in infants, such as irritability or inconsolable crying, to prevent adverse neurological consequences.

In summary, this case of NDM effectively demonstrates the complete clinical pathway from a non-specific, severe initial presentation to a diagnosis and highly specific, personalized treatment. It highlights the importance of considering rare metabolic disorders in acutely ill infants and underscores the central role of genetic and functional testing in modern diabetes care. The successful transition from insulin to oral sulfonylurea therapy exemplifies the concept of precision medicine, offering a simpler and more effective treatment that improves glycemic control and has the potential for better

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neurodevelopmental outcomes. This case reinforces that a deep understanding of the pathophysiology of NDM is crucial for optimizing patient management and outcomes [8, 10-12].

4. Conclusion

This case emphasizes the importance of considering Neonatal Diabetes Mellitus (NDM) in infants presenting with persistent hyperglycemia and severe non-specific symptoms such as respiratory distress. Functional testing with C-peptide proved pivotal in predicting sulfonylurea responsiveness, enabling a successful transition from insulin infusion to oral glibenclamide. This highlights the value of precision medicine in optimizing management. Early recognition, genetic evaluation, and dynamic, multidisciplinary long-term care are essential to improve both metabolic and neurodevelopmental outcomes.

Institutional Review Board Statement:

The Institutional Review Board of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, reviewed this case report and determined that formal ethical approval was not required. A waiver was granted. Written informed consent for the publication of clinical information was obtained from the patient's parents.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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