Case Report: Microdosing Insulin and Sulfonylureas in the Management of KCNJ11 Associated Neonatal Diabetes Mellitus

Perera, I., Sherwood, B., Jensen, B., Legard, C., Patel, H., Pediatrics Department, Carilion Roanoke Memorial Hospital, Roanoke, VA 24014, USA & Edward Via College of Osteopathic Medicine

Introduction and Objectives

Neonatal Diabetes Mellitus (NDM) or persistent hyperglycemia within the first 6 to 12 months of life, affects approximately 1 in 90,000 to 160,000 live births, with 31% of all preterm disease linked to monogenic etiologies[1-3]. 40% of NDM patients are responsive to oral sulfonylureas (SUs) due to mutations of ABCC8 or KCNJ11[1-5]. Oral SU therapy remains the mainstay of treatment for NDM; although, they are traditionally only dosed and approved for hyperglycemic control in adults[2,6]. Current treatment regimens suggest starting with subcutaneous (SQ) insulin, then transitioning to high dose SU at 1mg/kg/day, as most appropriate for patients with KCNJ11 NDM[6-9].

The primary aims of this research are to:

- Describe the case of a premature newborn with an initially undifferentiated class of NDM.
- Discuss the microdosing approach for both insulin and SU-based therapy.
- Develop a decision tree for the approach to the hyperglycemic newborn.

Our Case

A male neonate was born at 27 weeks, post-perinatal betamethasone administration, via emergency cesarean section due to complete placenta previa and hemorrhage. Neonatal resuscitation was required for Apgars 3, 6, and 7 (at minute 1, 5, and 10, respectively). He was found to be hyperglycemic, was started on empiric intravenous (IV) Ampicillin and Gentamicin for sepsis rule-out, and required intubation for respiratory support.

On day 1 of life (at an outside facility), he was hyperglycemic between 250 and 350 mg/dL while on IV dextrose-10 (D-10). This was reduced to D-5, trophic feeds were started, and he was started on Humulin 0.1 units/kg/dose subcutaneously (SQ). Blood cultures returned positive for coagulase negative Staphylococcus and thus Vancomycin was started. Feeds were fortified to 26 kcal/oz and IV D-5 was transitioned to ½- normal saline. The patient was transferred to our facility, for persistent hyperglycemia (229 to 266) and glucosuria despite fluid changes and SQ insulin increases.

On admission, SQ insulin was converted to 0.007 units/kg/hr insulin drip for better titration. Each day, continuous feeds were increased by 0.5 mL/hr until reaching 9.5 mL/hr. At that point, an increasing 5 mL BID was transitioned to oral feeds each day for three days. Genetic testing confirmed the KCNJ11 mutation and thus, NDM diagnosis, leading the team to start 0.1 mg/kg Glyburide suspension and weaning the IV insulin. Eventually, Glyburide was also able to be weaned and discontinued. The patient was discharged at the corrected gestational age of 38 weeks and 1 day with instructions to begin at-home glucose monitoring and to follow up with both Endocrinology and Neurodevelopmental for close evaluation of diabetes or developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome.

Of note, further discussion with the family revealed that the patient's father was also born preterm (at 25 weeks gestation) and diagnosed with NDM. He remained in the neonatal intensive care unit for 7 months and later developed Type 1 Diabetes Mellitus (DM). Parents further report a strong family history of DM.

Discussion

NDM linked to KCNJ11 is typically diagnosed at a median age of 9.6 weeks, with diagnosis before 1 month of age in 30% of cases and between 1 and 6 months in 66% of cases[1,2]. Our 27 week old was diagnosed at 6.3 weeks despite multiple confounders in his neonatal course, such as perinatal betamethasone administration, multiple suspected infections with potential sepsis, and the likelihood of increased counter-regulatory hormones.

Initial treatment of neonatal hyperglycemia favors proper maintenance of caloric intake balanced by insulin supplementation, that is titrated for the restoration of normal weight without leading to increased insulin resistance[2,10]. Awaiting genetic confirmation prior to starting SUs or starting empiric SUs as a trial are both accepted approaches to NDM of undifferentiated etiology[5,6]. It is also important to appreciate the narrow therapeutic index of insulin-based treatment in these young patients, as episodes of hyper- or hypoglycemia are detrimental to early development[2,10].

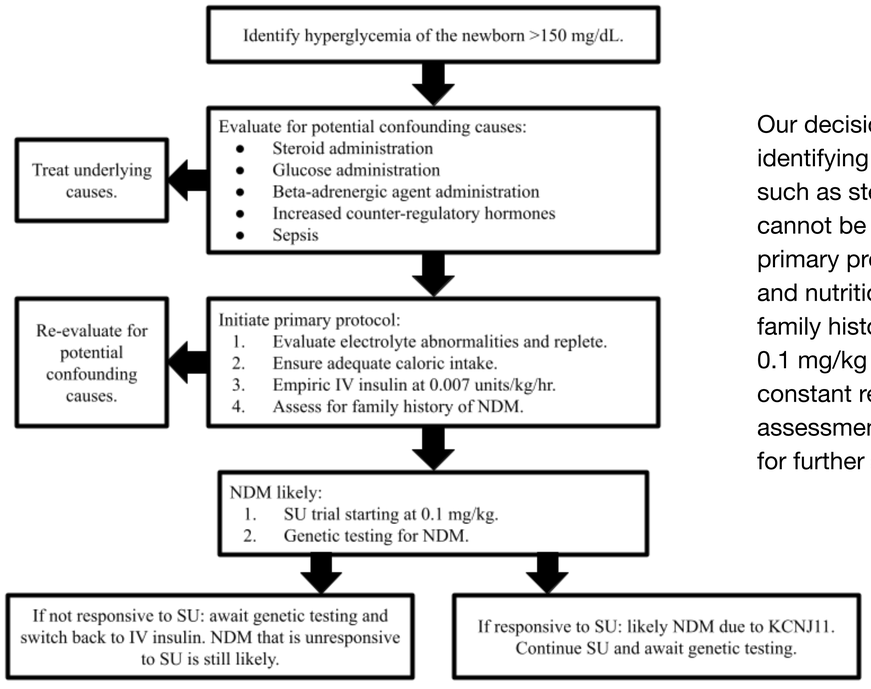

Figure 1. Newborn Hyperglycemia Decision Tree for Neonatal Diabetes Melitus

Our decision tree **(Figure 1)**, recommends first identifying confounding causes of hyperglycemia, such as steroids or sepsis. If newborn hyperglycemia cannot be contributed to these variables, initiate the primary protocol: evaluating the patient's electrolytes and nutrition, starting IV insulin, and assessing for family history. If NDM appears likely, begin SU trial at 0.1 mg/kg dose and send for genetic testing. Ensure constant re-evaluation of blood sugars for assessment of efficacy, while utilizing genetic testing for further adjustment.

Conclusions

NDM is a fairly uncommon cause of newborn hyperglycemia; however, it is important to maintain a high level of suspicion. Our team recommends the implementation of the above algorithm as a methodologic approach to these patients. Additionally, the treatment of NDM; although, well documented, does not address the risk of overdose due to SQ insulin administration. Our case suggests quickly shifting or even foregoing SQ administration for titratable IV insulin, with a recommended initial dose of 0.007 units/kg/hr.

Acknowledgements

We are thankful to the patient and his family for allowing us to share this case with our colleagues in the hopes of raising awareness about Neonatal Diabetes Mellitus. Thank you for allowing us to participate in your care.

References and E-copy of Poster