Conclusions: One-third of pediatric HLH patients required insulin during their hospitalization for severe hyperglycemia likely secondary to multiple factors including glucocorticoid use, parenteral nutrition, inflammation, and severe illness. Insulin is typically started within 5 days of initiating steroid therapy, limited to IV infusions, and often is not needed by the time of discharge. Risk of mortality is very high.

Diabetes Mellitus and Glucose Metabolism

METABOLIC DISEASE IN CHILDREN

Inheritance of Mildly Activating ABCC8 Mutation From a Mother With MODY Causes Permanent Neonatal Diabetes Mellitus (NDM) in Two Siblings Who Also Carry a Second Inactivating Mutation: Genetic Testing Allows for Improved Treatment With Sulfonylureas (SU)

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Background: Heterozygous activating mutations in KCNJ11 or ABCC8 are the most common cause of neonatal diabetes (NDM). ABCC8 (SUR1) mutations more often cause transient NDM. Inactivating ABCC8 mutations can cause congenital hyperinsulinism (HI), but very rarely will such mutations be inherited together. Mildly activating KATP mutations can also be a cause of MODY, but even if genetic testing is considered, many commercial testing panels do not include these genes, despite the significant difference in treatment that can result due to sulfonylurea (SU) responsiveness.
Clinical Case: The proband was diagnosed with DM at 11 months old and fortuitously treated with SU for 3 years. He was switched to insulin and had poor DM control thereafter. Sister was diagnosed at 3.5 months old and had poor DM control on insulin. Mother was diagnosed with DM at 27 years old and treated with various medications including insulin. Genetic testing revealed that mother carried ABCC8 mutation R1380C previously described to cause transient NDM and/or later-onset DM consistent with her phenotype. Both children inherited this mutation from her and inherited a variant (L1148R) from their father without diabetes that has been reported in association with HI. The L1148R allele may reduce cell surface expression thereby increasing the relative expression and pathogenic effect of the R1380C allele that has not previously been described to cause permanent NDM.
We assessed SU responsiveness by measuring maximal beta-cell function through combined mixed meal and arginine testing. Mother exhibited easily detectable C-peptide levels at baseline that improved by SU treatment. In contrast, the children displayed almost undetectable baseline beta-cell function with variable response to SU: the sister who had been chronically poorly controlled on insulin therapy displayed barely improved C-peptide production, while her brother who had previously been treated with SU as an infant had markedly improved beta-cell function on SU. Within two months of continued treatment with high doses of SU only, he was able to start lowering his SU dose with improved glycemia. His sister was started on high-dose SU in addition to insulin, but continued to have difficulty adhering to her treatment regimen. Her blood sugar improved after the addition of long-acting GLP-1 agonist (liraglutide) but she later became pregnant and returned to insulin only. Her glycemic control improved when re-started on SU after pregnancy. The mother exhibited excellent DM on a lower dose of exclusive SU therapy.
Clinical Lesson: Genetic testing can dramatically alter management and must be pursued in both NDM and family members with diabetes later in life. Careful assessment of clinical characteristics along with genetic testing for segregation patterns in family members can greatly improve understanding of the causality of previous uncharacterized variants.

Diabetes Mellitus and Glucose Metabolism

METABOLIC DISEASE IN CHILDREN

Neonatal Hypo-Ketotic Hypoglycemia Secondary to Transient Hyperinsulinism: Diazoxide Responsiveness and Experience With Fasting Test After Treatment Withdrawal

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Introduction:: Transient neonatal hyperinsulinism (TNH) is frequently reported in neonates with stress factors (intrauterine growth restriction (IUGR), large for gestational age (LGA), perinatal asphyxia, infants of diabetic mother, etc.). Early recognition and treatment are prioritary to avoid neurological morbidity. **Objective:** Clinical, molecular characterization and treatment response in neonates with hypoglycemia due to transient hyperinsulinism admitted to a tertiary hospital Neonatal Unit from January 2015 to August 2020. **Materials and Methods:** Prospective cohort study. Newborns older than 7 days of age, with diagnostic criteria of hyperinsulinism: non ketotic hypoglycemia with detectable insulin, low free fatty acids, glucose infusion rate > 10mg/kg/min, and positive response to glucagon test, were recruited. **Results:** Out of 5374 patients admitted, 46 (0.85%) presented hypoglycemia secondary to TNH (57% males and 43% females). 78% were delivered by Cesarean section, 59% were European, 17% Latino-Americans, 11% Asians, 9% Africans, and 4% Arabs. 78% were preterm newborns (median 33 weeks gestational age), 70% had birth weights or heights <-1.6 SDS (medians: -1.8 SDS and -2 SDS, respectively). Median age at diagnosis was 22 days (IQE 10–29 days), and feeding was exclusively enteral. Median blood glucose at diagnosis was 37mg/dl (IQE 31-44mg/dl), median insulin: 3mu/ml, median ketonemia: 0.2mmol/L, GH: 15 ng/ml, Cortisol: 16 ug/dl and AAL: 75mg/dl. 90% received diazoxide (dose ranged between 5-10mg/kg/day), presenting as most prevalent side effects hypertrichosis (80%) and edema (13%). Diazoxide median treatment duration was 83 days (IQE 41–110). Response was positive in 100%, with fasting tests response yielding a glycemia > 60mg / dl after 10 hours of fasting