

THE IMPORTANCE OF GENETICS WHEN TREATING HYPERINSULINISM

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WHAT IS HYPERINSULINISM ?

- The leading cause of hypoglycemia in infants and children
- Excess secretion of insulin without regulation by glucose

WHY TEST GENETICS IN CHILDREN WITH HYPERINSULINISM ?

- Genetic mutations correlate with clinical pathology
 - Diffuse
 - Focal
- Genetic Syndromes may have a hypoglycemia component
 - Beckwith Wiedemann (Overgrowth)
 - Kabuki Syndrome
 - Soto Syndrome
 - Turner Syndrome

WHAT GENETIC TESTING CAN TELL US ?

- The type of hyperinsulinism
- Whether or not certain medications will be effective
- What the treatment course will most likely be

GENETICS

- Each person has 2 copies of each gene
 - 1 from their mother and 1 from their father
 - 46 chromosomes total- 23 pairs
- Heterozygous- inherited from one parent
- Homozygous- inherited from both parents
- De Novo- not previously seen in the family

INHERITANCE

- Autosomal: not sex related
- Sex-linked: on sex chromosome (X or Y)
- Autosomal Dominant: one copy of the gene in each cell is enough to cause the disorder. (carrier parents likely has HI, may not be aware). Each parent 50 %
- Autosomal Recessive: both copies of the gene in each cell have the mutation. Each child 25 %

HOW IS GENETIC TESTING OBTAINED ?

- Blood draw or saliva sample
- Ensure insurance approval prior to obtaining
 - Try to send during inpatient admission
- Send parental genetics with child's

WHERE SHOULD GENETICS BE SENT ?

- University of Pennsylvania
- University of Chicago
- Athena Labs
- Prevention Genetics- charge for parental genetics

GENETIC MUTATION INDICATIVE OF FOCAL HYPERINSULINISM

- Gene: ABCC8
- Zygosity: Heterozygous
- Inheritance: paternally inherited
- Recessive
- Loss of maternal allele

MANAGEMENT OF FOCAL HYPERINSULINISM

- PET Scan to locate lesion
- Resection of lesion
- Cure



A CASE OF DIFFUSE HYPERINSULINISM

- Patient: GW
- Gene: ABCC8
- Zygosity: Heterozygous
- Inheritance: De Novo
- Dominant

MANAGEMENT OF DIFFUSE HYPERINSULINISM

- Can medication be used ?
 - Review genetics
- Can glucose needs be met with enteral dextrose?
 - Nasogastric tube vs. Gastrostomy tube
- Glucose infusion rate (GIR) >10 mg/kg/min
 - 98 % Pancreatectomy
 - Will develop diabetes by adolescence

PHARMACOLOGIC TREATMENT OPTIONS FOR HYPERINSULINISM

- **Diazoxide:** works at the potassium channel (KATP)
 - Ashkenazi Jewish mutation- known recessive homozygous, potassium channel does not exist so diazoxide will not work
- **Enteral Dextrose**
- **Octreotide:** works at the calcium channel
- **Lanreotide:** works at the calcium channel

DIAZOXIDE (PROGLYCEM)

- **How Diazoxide works:**



- Allow the potassium channel of the cell to open
- The opening of the potassium channel inhibits the secretion of insulin

DIAZOXIDE MONITORING LABS

- CBC with differential
- Uric Acid
- Diazoxide level
- Basic Metabolic Panel (BMP)

DIAZOXIDE: SPECIAL CONSIDERATIONS

- Dosing: Diazoxide up to 15 mg/kg/day
- Cost
 - Made by Teva Pharmaceuticals
 - FDA mandates it be made
 - Prior Authorizations
 - Co-Pays
- Availability
- Taste

DIAZOXIDE SIDE EFFECTS

- Fluid Retention:
 - Diuril (Chlorothiazide): monitor BMP
- Excess hair growth
- Neutropenia

ENTERAL DEXTROSE

- GW did not respond to Diazoxide
 - Enteral dextrose
 - Gastrostomy tube placement
 - Octreotide injections at 8am and 2pm
 - Feeds via gastrostomy tube

OCTREOTIDE (SANDOSTATIN)

- **Method of Action:**
 - Works on the calcium channel
 - Inhibits insulin release
 - Also inhibits release of other endocrine hormones:
 - Thyroid hormone
 - Growth hormone

OCTREOTIDE SIDE EFFECTS

- Octreotide suppresses insulin and other hormones that make things grow
- **Monitoring:**
 - Thyroid labs
 - Growth factors
 - LFTs
 - Abdominal US

OCTREOTIDE: SIDE EFFECT MANAGEMENT

- Hypothyroidism
- Growth concerns
- Gallstones: Ursodiol

OCTREOTIDE ADMINISTRATION

- Dosing: Octreotide up to 15 mcg/kg/day
- Subcutaneous
- Concentration: Octreotide 200 mcg/ml
- Insulin pump
- Insulin syringe
 - conversion

OCTREOTIDE AND NECROTIZING ENTEROCOLITIS (NEC)

- Avoid Octreotide in children < 2 months
- Caution in former preemies

LANREOTIDE (SOMATULINE)

- Long acting form of Octreotide
- Dosing: Lanreotide 60 mg every 28 days
- Side effects and monitoring – same as for Octreotide
- “Deep Sub Cutaneous” injection
- Apply EMLA prior to injection

LANREOTIDE

- Get insurance approval
- Assure someone will give
- Stopping Octreotide
- Admission after 4th dose
- Assess for nodules



RESOURCES

- **Children's Hospital of Philadelphia website**
 - www.chop.edu
- **Congenital Hyperinsulinism International (CHI)**
 - <https://congenitalhi.org>
- **Mcknight@email.chop.edu**