CE 2.3 HOURS Continuing Education

Congenital Hyperinsulinism

Exclusive Human Milk and Breastfeeding

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ABSTRACT

Congenital hyperinsulinism is a genetic condition causing dysregulation of insulin and results in persistent hypoglycemia. The most common types are sulfonylurea receptor (*SUR1*), potassium inward rectifying channel (*Kir6.2*), glutamate dehydrogenase (*GDH*), and glucokinase (*GK*), with *SUR1* and *Kir6.2* being the most prevalent. It is imperative that these infants undergo diagnostic testing, which includes genetic, neonatal fasting study to induce hypoglycemia, glucagon stimulation, and imaging. Once a diagnosis has been made, surgical intervention may be needed to help regulate blood glucose levels. During this diagnostic process and as the infant is undergoing treatment, there may be little concern for the mother's feeding plan. Because human milk is the preferred form of nutrition for all infants, these mothers should receive prenatal counseling regarding the initiation and maintenance of milk supply. Parenteral nutrition may be necessary to maintain blood glucose to support human milk administration and breastfeeding.

Key Words: enteral nutrition, human milk, hyperinsulinism, hypoglycemia

The Surgeon General's Call to Action and the American Academy of Pediatrics urge healthcare providers to promote and support breastfeeding in any setting.[1,2] Depending on the patient scenario, healthcare providers are often encouraged to steer away from human milk and breastfeeding even though this is not the current recommendation. One of the most common scenarios is hypoglycemia that can lead to much debate between healthcare providers on proper management. The most common cause of persistent hypoglycemia in newborns and infants is congenital hyperinsulinism (CHI).[3,4] This is a genetic condition causing dysregulation of insulin secretion and occurs 1 in every 30,000 to 50,000 live births.[4,5] These infants present with lethargy, apnea, large for gestational age, and seizures. A high glucose infusion rate (GIR) is often needed to prevent hypoglycemia, apnea, and seizures. Without immediate medical management and correction of hypoglycemia, brain damage and death may ensue. For the purpose of this article, only CHI in the neonatal/infant period will be discussed along with exclusive human milk administration and breastfeeding.

There are several different types of CHI, but the most common are sulfonylurea receptor (*SUR1*), potassium inward rectifying channel (*Kir6.2*), glutamate dehydrogenase (*GDH*), and glucokinase (*GK*).[6] *SUR1* and *Kir6.2* are the most prevalent types, resulting in a dysfunctional K_{ATP} channel and overproduction of insulin from the β cell. In certain types of CHI, diazoxide (Proglycem, Merck and Company, Incorporated, Whitehouse Station, New Jersey), which inhibits pancreatic insulin release, is usually ineffective and a pancreatectomy is needed to assist in blood glucose regulation. This is because the K_{ATP} channel may not exist or because the channel does not open. Within K_{ATP} HI there are 2 forms, focal and diffuse disease.[6] Focal disease, a localized lesion, consists of one recessive mutation inherited from the father and loss of heterozygosity from the mother.[4,6] Diffuse disease occurs when there are 2 autosomal recessive genes.[6]

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Glutamate dehydrogenase hyperinsulinism results in hypoglycemia caused by the loss of inhibitory control of *GDH* by β cells.[6] This results in excessive insulin release and ammonia production. With *GDH* CHI, diazoxide is usually effective. Last, *GK* hyperinsulinism results in hypoglycemia when there is constant secretion of insulin and there is an inability for the pancreas to stop production.[6] Infants with *GK* CHI can respond to diazoxide but may also require a pancreatectomy. For both *GDH* and *GK* hyperinsulinism, diazoxide is effective because the K_{ATP} channel is present and can be opened to allow the medication to work.

DIAGNOSIS

The diagnosis of CHI consists of genetic testing, a fasting study with glucagon stimulation, and imaging through computed tomography (CT) scan and positron emission tomography (PET) scan. Genetic testing is performed on both parents and the infant. This testing will determine the inheritance pattern (eg, recessive, autosomal dominant, loss of heterozygosity).[5,6] With recessive inheritance, there is an affected gene that comes from each parent. Because each parent is a carrier, the infant must have 2 affected genes to have CHI. Autosomal dominant inheritance occurs when there is one affected gene from either parent, which ultimately results in CHI in the infant. Only for focal hyperinsulinism, there is loss of heterozygosity. Typically this occurs when the infant receives 1 gene from the mother and 1 affected gene from the father. But in CHI, there is loss of the mother's protective allele and the father's recessive affected gene becomes duplicated.[6]

A neonatal fasting study is performed to induce hypoglycemia and once the infant's blood glucose level reaches less than 50 mg/dL, laboratory studies are collected.[5] The following laboratory studies are needed: confirmatory blood glucose, ammonia, basic metabolic panel, free fatty acids, insulin level, cortisol, plasma lactate, β-hydroxybutyrate, insulin-like growth factor binding protein–1, growth hormone, and c-peptide.[6] Once the laboratory studies are collected, a glucagon stimulation test is performed. Glucagon 1 mg is intravenously given and blood glucose levels are obtained every 10 minutes for 40 minutes. If there is not a significant rise in the blood glucose level (↑15-20 mg/dL) by 20 minutes postadministration or once the 4 blood glucose levels have been obtained, feedings or parenteral fluids should be resumed at the pretesting GIR.[5]

The CT scan is used to determine the anatomy of the pancreas and will be used with the PET scan. The PET scan is used to determine if the lesion in the pancreas is focal or diffuse. Neuroendocrine cells, like β cells, have the ability to uptake the catecholamine precursor, l-dihydroxyphenylalanine (L-DOPA), and convert it into dopamine by L-DOPA decarboxylase. The radionuclide, 18-fluoro-L-3, 4-dihydroxyphenylalanine (ie, ^{18}F-Dopa), is administered and there is uptake into the β cells of the pancreas.[7]

DIAGNOSTIC RESULTS

For infants with CHI, there will be a decreased free fatty acid level, decreased β-hydroxybutyrate level, possibly elevated insulin level, and elevated c-peptide level from the neonatal fasting study.[5] Once glucagon is administered, there should be a rise in the blood glucose by 15 to 20 mg/dL, which generally occurs in the first 20 to 30 minutes after the dose is administered.[5,6] When the PET scan is performed, the absorption of ^{18}F-Dopa will determine the location and size of the lesion. If the lesion is focal, there will be a concentrated number of β cells; therefore, the area containing the lesion will generate a stronger gamma-ray signal.[5,7] If there is dispersed accumulation of ^{18}F-Dopa, the lesion is considered to be diffuse.[5,7]

Once the diagnosis has been confirmed and the need for surgery is identified, the infant will be transported to the operating room. At that time, a laparotomy is performed and the information from the CT scan and PET scan is used to assist in lesion location. Intraoperative biopsies are taken from the pancreas without the use of cautery.[8] The biopsies are delivered to the pathology department for interpretation. A focal lesion will be resected and a Salem sump will be in place postoperatively. Diffuse disease requires a near total pancreatectomy in addition to gastrostomy tube placement and Salem sump placement postoperatively for gastric decompression.

TREATMENT

Medical and surgical management for CHI are used in hypoglycemia management. Medical management consists of parenteral administration, enteral dextrose administration, and/or pharmacologic therapies.[5] It is important to remember that enteral feeding is not a way to manage hypoglycemia, but used in addition to parenteral fluid and/or pharmacologic therapies. There is much focus on the dextrose infusion to maintain euglycemia; however, parenteral fluid administration can lead to fluid overload, therefore consistent assessment of intake and output is necessary. Fortification of human milk may be needed to meet protein requirement. For infants aged 0 to 6 months, an average protein requirement is more than 1.5 g/kg per day and for those aged 6 to 12 months more than 1.2 g/kg per day.[9] Ensuring adequate protein stores will help support growth of lean body mass, maintain visceral protein stores (albumin and prealbumin), and

support growth in length. Calorie needs are usually easily met, if not exceeded, between dextrose infusions and feeds, with primary calorie provision coming from carbohydrates.

Typical pharmacological therapies consist of diazoxide, octreotide, and glucagon. Diazoxide (Proglycem) is a first-line agent and a K_{ATP} channel agonist that increases the blood glucose level by inhibiting the release of insulin from the pancreas.[4] The most common side effects of this medication are decreased excretion of sodium and water resulting in fluid retention that is managed with diuretics and hypertrichosis.[10]

Octreotide (Sandostatin, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey) is a somatostatin analog that inhibits insulin secretion distal to the K_{ATP} channel by inducing hyperpolarization of β cells. With octreotide, there is decreased splanchnic blood flood placing the infant at an increased risk for necrotizing enterocolitis, inhibition of several hormones (eg, glucagon, growth hormone, thyroid, serotonin, gastrin), and decreased gallbladder contractility and bile secretion.[10,11]

Glucagon (GlucaGen, Novo Nordisk A/S, Denmark) activates adenylate cyclase and increases cAMP. There are no major adverse effects of the medication, and it aids in decreasing the GIR requirement and maintaining euglycemia.[10]

Surgical management is considered when medical management cannot maintain euglycemia. A laparotomy is performed, the pancreas is identified, and intraoperative pancreatic biopsies are taken without the use of cautery.[4,5] A pediatric pathologist interprets the biopsies intraoperatively. Focal lesion can be found in the head, neck, body, or tail of the pancreas and will be resected. If the focal lesion terminates in the head of the pancreas a Roux-en-Y pancreaticojejunostomy is needed.[8] For infants with a focal pancreatectomy, a Salem sump will be in place postoperatively for gastric decompression. Diffuse disease requires a near total pancreatectomy in addition to gastrostomy tube placement and Salem sump placement postoperatively for gastric decompression. A gastrostomy tube is placed because of poor oral feeding and possible need for long-term continuous enteral dextrose infusion.[5]

PROGNOSIS

For those infants with focal CHI, medical management and possible surgical management have a great outcome. If surgical management is needed and a focal pancreatectomy is performed, CHI is considered to be cured.[4] This is verified by a repeat neonatal fasting study, which shows elevated ketones on laboratory results. For those infants where medical management fails and diffuse CHI is present, then surgical management is often pursued. A near-total pancreatectomy is performed to help prevent hypoglycemia and brain damage, but it is often not a cure.[4,12] About half of these infants will have persistent hypoglycemia requiring enteral dextrose infusion via gastrostomy tube, about a third will require insulin administration, and only a sixth of these infants will require no medical therapy (The Congenital Hyperinsulinism Center at CHOP, written communication, February 10, 2014).

There are multiple studies that have evaluated hypoglycemic brain injury. When severe hypoglycemia ensues, neuronal loss in the superficial cerebral cortex, dentate gyrus, hippocampus, and caudate nucleus occurs. If hypoglycemia is left untreated, there are profound neuromuscular outcomes, including mental retardation, cerebral palsy, seizure disorder, microcephaly, spasticity, and ataxia.[13,14] In addition to these findings, approximately one-third have developmental delay.[14] It is recommended that a neurodevelopmental screening is completed at 12 to 18 months and at 5 years of age.

EXEMPLAR CASE REPORT

A 36-week and 1-day old female was born to a 36-year-old G3 P1→2 mother. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. A birth weight of 4.12 kg was obtained. After birth, she was admitted to the NICU because of a prenatal diagnosis of CHI. The parents underwent preemptive genetic testing at 10 weeks' gestation because of their Eastern European Jewish descent. Genetic testing confirmed that both the mother and father were carriers for the *SUR1* gene. Therefore, the mother underwent chorionic villus sampling testing at 12 weeks' gestation, which revealed that the fetus was positive for the *SUR1* gene.

Immediately after delivery, the newborn was started on D10W parenteral fluids, admitted to the NICU, and allowed to take orally ad lib with human milk. See Table for human milk transfer volumes during admission. Because of hypoglycemia, she required background parenteral fluids to maintain euglycemia.[5] At 2 days of age, the newborn underwent the neonatal fasting study and glucagon stimulation test.[5] The neonatal fasting study results were consistent with CHI and she was responsive to glucagon. On day 6 of life, she was started on a glucagon infusion to assist in maintaining her blood glucose levels.[5] Her dextrose requirement increased over time and her GIR before going to the operating room was 21 mg/kg per minute with D30 hyperalimentation. Her CT scan revealed the anatomy of her pancreas and her PET scan revealed that she had diffuse disease.[5,7] On day of life 13, she underwent a 95% pancreatectomy and gastrostomy tube placement.

Postoperatively she took nothing by mouth on hyperalimentation and intralipids at a GIR of

TABLE. Human Milk Transfer Volumes

Day of Life	Range of Human Milk Transferred
0	Mouth care with human milk to 3 mL
1	6 to 10 mL
2	0 to 6 mL
3	15 to 30 mL
4	0 to 50 mL
5	10 to 30 mL
6	10 to 50 mL
7	48 to 60 mL
8	30 to 65 mL
9	25 to 60 mL
10	20 to 60 mL
11	10 to 55 mL
12-17	Nothing by mouth
18/postoperative day 3	1/3 volume feedings (20 mL every 3 h)
19/postoperative day 4	2/3 volume feedings (40 mL every 3 h)
20/postoperative day 5	Full-volume feedings (60 mL every 3 h)

8 mg/kg per minute. An insulin infusion was started upon return to the NICU because of transitional hyperglycemia. On postoperative day 3, one-third volume feedings were started at 20 mL every 3 hours of human milk 20 cal/oz via bottle/breast or gastrostomy tube. Once feedings were tolerated at this volume, the GIR was decreased to 5 mg/kg per minute. On postoperative day 4, feedings were advanced to two-thirds at 40 mL every 3 hours of human milk 20 cal/oz. Once feedings were tolerated at this volume, the GIR was decreased to 2 mg/kg per minute. On postoperative day 5, feedings were advanced to full volume at 60 mL every 3 hours of human milk 20 cal/oz. She remained on a GIR of 2 mg/kg per minute until postoperative day 6 because of increased frequency of emesis. Also, on postoperative day 6, the insulin infusion was also discontinued. Once feedings were tolerated, the newborn was transferred to the endocrinology service for further medical management.

DISCUSSION

For infants who present with persistent hypoglycemia, it is imperative to rule out CHI. Endocrinology services should be consulted not only to assist in the management of the patient, but also to interpret the endocrinology studies.[5] Congenital hyperinsulinism is challenging to manage; however, the enteral route should not be used to maintain euglycemia.[5] This is crucial in providing optimal care for this patient population. These infants will require a long-term central catheter for administration of high dextrose containing parenteral fluids.

In addition to maintaining blood glucose levels parenterally, there is evidence that human milk should be utilized without supplementation from formula or other substrates enterally.[1,2,15] It is essential that mothers receive evidence-based lactation support and care and that there are adequate resources (breast pump, milk storage, etc.) available so that her human milk and breastfeeding goals can be achieved.

The Surgeon General's Call to Action urges us as healthcare providers to promote and support breastfeeding and to use skilled lactation consultants to establish routine human milk and breastfeeding practices within healthcare organizations.[1] This includes providing prenatal counseling on feeding decisions and providing families with the science of human milk and the risks of infant formula so an informed decision can be made.

Because the fetus was diagnosed in utero with CHI, the family was able to deliver in the special delivery unit at the Children's Hospital of Philadelphia. This mother received an extensive lactation consultation prenatally to determine her breastfeeding and human milk goals and receive instruction on the initiation of pumping/breastfeeding postpartum. The family was supported throughout the entire hospital admission by decreasing mother-infant dyad separation and by having her use a hospital-grade breast pump while the infant was taking nothing by mouth.[16]

RECOMMENDATIONS FOR PRACTICE

The use of human milk has been associated with better cognitive outcomes and a decrease in infant mortality rate.[2] For vulnerable infants, like those diagnosed with CHI, human milk is recommended for enteral feedings. The protective properties facilitate the healing process after surgery, as well as long-term support for neurodevelopmental outcomes since these infants are at high risk for developmental delay.[14] The authors recommend the use of dextrose-containing parenteral fluids to assist in blood sugar regulation and the use of human milk for nutritional aspects.

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