

---

**CONGENITAL HYPERINSULINISM  
FAMILY CONFERENCE  
2003**

---

**Held  
June 20 –21 2003  
at the Sheraton City Hotel  
in Philadelphia**

**Hosted by  
The children's hospital of Philadelphia**

**Report  
October 2004**

*Prepared by Isabel Calderón  
Medical revision by the speakers  
English revision by Noel and Gabrielle Flynn*



## TABLE OF CONTENTS

<b>Table of contents</b> _____	<b>iii</b>
<b>Introduction</b> ( <i>Julie Raskin</i> )_____	<b>1</b>
<b>Normal Beta cell function and how defects in the function of a potassium channel cause HI</b> ( <i>D<sup>r</sup> Lydia Aguilar</i> ) _____	<b>3</b>
<b>Dominant forms of HI</b> ( <i>D<sup>r</sup> Andrea Kelly</i> ) _____	<b>6</b>
<b>Genetics of HI</b> ( <i>D<sup>r</sup> Andrea Kelly</i> ) _____	<b>9</b>
<b>Arterial stimulation with venous sampling (ASVS) in congenital hyperinsulinism</b> ( <i>D<sup>r</sup> Robin Kaye</i> ) _____	<b>11</b>
<b>Surgical treatment of HI</b> ( <i>D<sup>r</sup> Scott Adsick</i> ) _____	<b>13</b>
<b>Non-surgical treatment of severe hyperinsulinism and its long term outcome</b> ( <i>D<sup>r</sup> David Gillis</i> ) _____	<b>17</b>
<b>Hypoglycemia, brain injury and developmental consequences</b> ( <i>D<sup>r</sup> Lawrence Brown</i> ) _____	<b>26</b>
<b>Feeding issues in children with HI</b> ( <i>D<sup>r</sup> Maria Ramsay</i> ) _____	<b>31</b>

## INTRODUCTION

In the summer of 2003, At the Congenital Hyperinsulinism (HI) Family Conference, HI families from around the world gathered together in Philadelphia to learn more about the disease that affects their children. Physicians, researchers, and other medical specialists who specialize in HI provided parents with an opportunity to broaden their knowledge of HI, in order to better the lives of their children. Parents also shared useful and practical information with each other.

The following pages consist of summaries of some of the presentations given at the Conference. The range of topics discussed at the Conference was very large. Parents were introduced to all aspects of the condition, from an explanation of the pathology involved to treating the feeding issues that result from the condition; from managing the medically responsive child to surgical treatment. In all, there were eighteen sessions providing parents with a range of extremely important information. Among the speakers were leaders in the field of HI from medical institutions around the U.S. as well as abroad. Due to the proximity of the Children's Hospital of Philadelphia, one of the leading centers for the treatment of HI, many HI specialists at CHOP were able to present at the Conference.

Speakers at the Conference included N. Scott Adzick, MD; Lydia Aguilar-Bryan, MD, PhD; Lawrence Brown MD; David Gillis, MD; Adda Grimberg, MD; Khalid Hussain, MD; Dr. Robin Kaye, MD; Dr. Andrea Kelly, MD; Maria Ramsay, PhD; Dr. Charles Stanley, MD; Linda Steinkrauss, RN, MSN; Laura Steinmuller, RN, MSN; Mariko Suchi, MD, PhD; Patrick Terry; Dr. Paul Thornton, MD; Samantha Zucker RD.

We are also providing you with a few HI attachments in addition to the Conference summaries for those interested in learning more about HI including:

1. A flyer on joining an HI online discussion and support group;
2. An order form for a film on HI entitled *HIstories, Faces of Congenital Hyperinsulinism*, based on footage from the Conference;
3. A questionnaire for the HI reference chart compiled by Isabel Calderon.

By Julie Raskin

*Note: The text that follows reflects the opinion of the author only*

## **NORMAL BETA CELL FUNCTION AND HOW DEFECTS IN THE FUNCTION OF A POTASSIUM CHANNEL CAUSE HI**

Lydia Aguilar-Bryan, MD  
Baylor College of Medecin, Houston USA

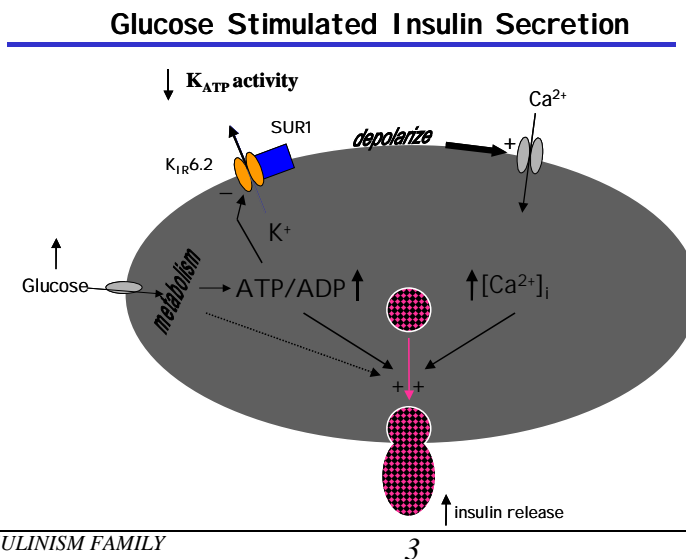
To understand what causes hyperinsulinism and what can be done to control it, we need to have a basic understanding of how the  $\beta$  cells from the pancreas regulate glucose stimulated insulin secretion.

It is important to give some background, before we get into the regulation of insulin release. (1) Of all the channels (pores) that are present in the plasma membrane of the  $\beta$  cell, the ATP-sensitive  $K^+$  channel ( $K_{ATP}$ ) is the most important, because it sets the resting membrane potential and anything that changes its activity, will result in changes in insulin secretion. (2) These channels are formed by two sub-units, SUR1 or the high affinity sulfonylurea receptor and  $K_{IR6.2}$ , which forms the  $K^+$  selective pore. (3) Compounds that are use to treat hyperglycemic states like diabetes, and hypoglycemic states like HI, bind to the SUR1 receptor.

### Physiology:

The sequence of events that produces the stimulation of insulin release by glucose occurs in the following way:

After we have a snack or a meal, glucose increases in the blood stream and enters the  $\beta$  cell. Once in the  $\beta$  cell, glucose is metabolized and as a result, it changes the nucleotide concentration (ATP/ADP) inside of the cell. This change will result in the closure of the  $K_{ATP}$  channels, which in turn will bring about the opening of the calcium ( $Ca$ ) channels. Calcium will enter the cell and promote release of insulin into the blood stream. In brief, changes that bring about the closure of the  $K_{ATP}$  channel will stimulate insulin release and changes that result in the opening of the channel will results in the inhibition of insulin release. The diagram below illustrates the steps involved in glucose stimulated insulin secretion.



The main goal in the treatment of HI is to inhibit insulin release. This can be achieved by using compounds that will act on the  $K_{ATP}$  channel, the Calcium channel or other sites within in the plasma membrane, like somatostatin.

#### Clinical Treatment:

Diazoxide, which is in general the initial treatment, acts on the  $K_{ATP}$  channel, in what looks like two different ways. One is by increasing the open probability of the channel and the second one seems to be related to producing an increase in the number of channels that traffic to the plasma membrane.

Nifedipine is a Calcium channel blocker, so this will mimic the second step after you open the  $K_{ATP}$  channel; the response has been very poor in many of the patients.

The third compound that is used is somatostatin, which is a well-established inhibitor of insulin release. Although its place of action is not clear, it is possible that it exerts its effect by acting on a different kind of  $K^+$  channel, also present in the plasma membrane.

The response to the different compounds is variable, and part of this variability may depend on the kind of mutation that the patient has.

#### Mutational Analysis:

There are several genes (Glucokinase, Glutamate Dehydrogenase and SCHAD) that can give the HI phenotype, but about 50% of the cases are due to mutations in Sur1 and  $K_{IR6.2}$  genes, the two subunits that form the  $K_{ATP}$  channel. About 100 mutations have been identified, with 90% of them being in SUR1 and a small percentage in  $K^+$  pore. Defects in the Sur1 gene affect channel activity in different ways, including complete absence of function. Because this altered activity causes the plasma membrane to depolarize, as mentioned in the figure, the result will be stimulation of insulin release, which is what the children with HI present.

The Sur1 gene is composed of 1581 amino acids divided into 39 exons. To be able to identify the mutation responsible for the disease, we need to look at all these exons, plus the one from the  $K^+$  pore. It is important to make clear that this is a long, time consuming and expensive task.

To facilitate the nomenclature or cataloging of the different proteins that are involved, we suggested that the following names would be easier to understand, "HI-SUR1" and the "HI- $K_{ir6.2}$ " mutations.

Once these mutations have been identified, intense research is going on to try to understand the mechanisms by which the change alters channel function. For this we express the mutation in a cell system that we know does not have the channel and we test their presence and degree of activity by stimulating the channel function with the metabolites and compounds that we know stimulate or inhibit insulin secretion.

The research results show that we have mainly two types of alterations, one in which the response to the changes in the ATP/ADP ratio is variable, and most or all those children respond to clinical treatment. The other ones seem to have broken channels in the plasma membrane or complete

absence. Most of these ones do not respond to clinical treatment and require a pancreatectomy or a very strict dietary/glucose infusion treatment, to avoid hypoglycemia.

To better understand and manipulate the system we decided to create a Knock Out (KO) mouse. This would be a mouse that does not have these channels present, like the children with HI. To our surprise the Sur1KO mice have a normal body weight at birth, have a normal glucose level unless stressed and show mild glucose intolerance. In comparison with the HI-SUR1 child, the differences are overwhelming and we are trying our best to understand why....

**Q1:** Most babies born with PHHI are large and many have an IDM appearance – but this was not asked at birth. How do you explain that a baby having a normal weight turns out to have a severe form of PHHI?

**A:** We need to keep in mind that it is never the case where every infant has always the same presentation at birth. The degree of variability/heterogeneity in this disease is enormous and there are still many aspects of it that we do not understand.

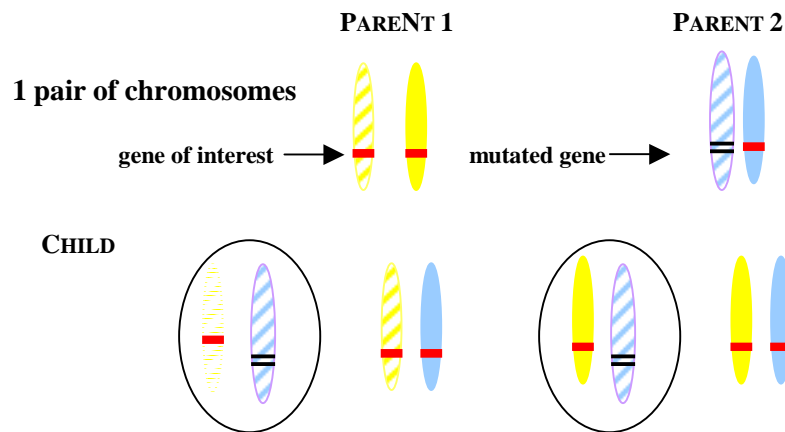
## **DOMINANT FORMS OF HI**

Andrea Kelly, paediatric endocrinologist  
Children's Hospital of Philadelphia, Philadelphia USA

The three known forms of dominant HI are:

- Glucokinase-HI,
- GDH-HI (Hyperinsulinism/hyperammonemia syndrome)
- Potassium channel-HI (Sur1/Kir6.2).

A disorder that is inherited in an autosomal dominant fashion requires only one of the two normally inherited genes to be mutated. Autosomal dominant HI may arise from a mutation inherited from a parent (dominant inheritance). Note that a parent might have the defect and not have readily apparent symptoms of HI. The figure below shows a dominant inheritance pattern.



**Figure 1 : Dominant inheritance pattern : there are 4 possible combination of genes inherited from parents. Two of the four combinations will result in the child being affected.**

Another possible mechanism for having an autosomal dominant form of HI is for a mutation to occur spontaneously during fetal development (sporadic mutation). In this case neither of the parents carries the mutation. The likelihood of having a second child with a spontaneous mutation is highly improbable.

In order to understand the different forms of dominant HI, understanding how the beta-cell functions is important. When the potassium channels ( $K_{ATP}$ ) on the beta-cell are closed,  $Ca^{++}$  enters the cell and causes insulin secretion. This mechanism is known as the potassium-channel pathway of insulin secretion.

Glucokinase (GK) is an enzyme that serves as the glucose sensor or “thermostat” for the beta-cell. In normally functioning beta-cells, when blood glucose is above 70 mg/dl (3.8 mmol/l), GK

is active and causes insulin secretion via the closure of the potassium channels. On the other hand, when blood glucose is below 70 mg/dl (3.8 mmol/l), GK is inactive and insulin secretion is suppressed. When a mutation increases the normal function of the glucokinase enzyme it can result in glucokinase-hyperinsulinism (GK-HI). Glucokinase activity is turned off at a lower blood glucose level than normal. This type of HI is thought to be diazoxide-responsive. Only a few cases of GK-HI have been identified.

Glutamate dehydrogenase (GDH) is an important regulator of amino-acid stimulated insulin secretion and is activated by leucine (an amino acid). Activation of GDH leads to energy production inside the beta-cell which in turn leads to closure of the potassium channels and, thus, insulin secretion. In glucokinase dehydrogenase-HI (GDH-HI) or HI/HA syndrome, a gain of function mutation of GDH is present. This type of HI is leucine- and protein-sensitive. A clue to the diagnosis of GDH-HI is the presence of low blood sugars after eating; these low blood sugars arise as a result of eating protein. Leucine, a component of protein, is the specific trigger for the hypoglycemia. A normal child has no insulin response to leucine and does not become hypoglycemic with protein ingestion. GDH-HI is responsive to diazoxide. Avoidance of pure protein meals and eating carbohydrates prior to protein are necessary for GDH-HI treatment. The elevated ammonia levels in this form of HI may be due to over-activity of GDH in the liver, the usual site for ammonia metabolism. In the setting of a gain of function mutation of GDH, excess ammonia production and impaired ammonia detoxification are thought to occur.

Potassium channels, also known as  $K_{ATP}$  channels, are located on the membrane of the beta-cell and respond to energy states within the beta-cell.  $K_{ATP}$ -HI occurs when potassium channels are absent or do not work properly. These defects have the same consequences as having channels that are always closed:  $Ca^{++}$  enters the beta-cell unabated which in turn causes excessive/unregulated insulin secretion.

Previously diffuse HI was thought to arise only through recessive mutations. Focal lesions due to loss of heterozygosity in setting of one inherited  $K_{ATP}$  mutation are another form of as  $K_{ATP}$ -HI. Recent studies have shown that dominant mutations of the SUR can lead to diffuse HI. Recessive  $K_{ATP}$ -HI and focal  $K_{ATP}$ -HI do not respond to diazoxide. Dominant  $K_{ATP}$ -HI may respond to diazoxide.

The potassium-channel pathway is probably only one of a number of pathways for insulin secretion. The specifics for these other pathways have yet to be fully identified.

**Q1:** Which types of food have more leucine

**A:** All protein foods: steak, eggs, chicken...

**Q2:**  $K_{ATP}$ -HI is not affected by leucine like GDH-HI. Is there a difference in the management of GDH-HI and  $K_{ATP}$ -HI?

**A:** Both types of HI are managed the same way. Both should avoid pure protein meals.

**Q3:** What is the inheritance pattern of focal HI.

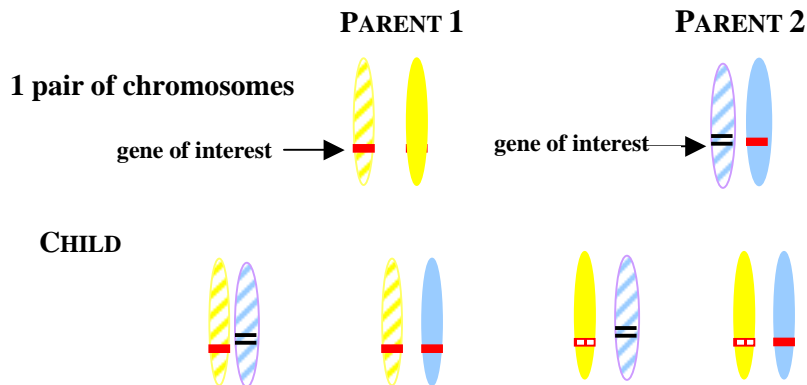
**A:** SUR1 is located on chromosome 11. In focal HI, the SUR mutation is inherited from the father. Then, for unknown reasons, the chromosome 11 that the child has inherited from the mother is lost in a subset of beta-cells. This subset of beta-cells is left with one abnormal SUR. On chromosome 11 from the mother, growth-suppressing factors normally are active. On chromosome 11 from the father, growth-promoting factors are usually active. The presence of these growth-promoting factors in the absence of growth-suppressing factors allows growth of these beta-cells which express the abnormal potassium channel.

## **GENETICS OF HI**

Andrea Kelly, MD

Children's Hospital of Philadelphia, Philadelphia USA

Each of us has 23 pairs of chromosomes (or 46 chromosomes) and two copies of each gene. Each parent gives only 1 of his/her two copies of the gene to the child. There are four possible combinations of genes inherited from parents. The figure below illustrates inheritance pattern.



**Figure 1: normal inheritance pattern**

When one parent has a gene having a dominant mutation, two out of the four (50 %) possible combinations of inheritance will result in the child being affected (see Dominant forms of HI). Note that only one of the two genes is affected (versus recessive inheritance).

In recessive inheritance both of the genes need to be mutated in order for the disease to be expressed. If only one recessive gene is present, the disease will not be expressed because the normal gene will “hide” the expression. For recessive inheritance to take place, both parents need to have at least 1 genetic mutation. If both parents have one mutated gene and, thus, do not have the disease, out of the four possible combinations of inheritance, only one combination (25 %) will result in the child being affected.

If one parent has the disease and the other carries the mutation, then 50 % of the combinations of gene inheritance will result in the child being affected.

If both parents have the disease a 100 % chance of the children being affected exists.

Recessive inheritance may also cause disease when loss of heterozygosity occurs. The child inherits only one recessive mutated gene (from one of his parents) and for some reason, the normal gene will be absent in subset cells (blood DNA may be ok but other body cells may be affected). The recessive gene will thus be expressed. The risk of additional children being

affected in this pattern depends of the rate of loss of heterozygosity. An estimate is 1 in 400. Recessive inheritance with loss of heterozygosity is found in potassium channel HI.

**Q1:** What causes of spontaneous mutation

**A:** There are known factors of spontaneous mutations but most likely this happens during cell division. During cell division, DNA breaks and mistakes may take place during the reparation processes. It is unlikely that the spontaneous mutation is due to something the mother did during pregnancy.

**Q2:** Can prenatal genetic testing be done?

**A:** Only when the genetic mutation is already known. The results can then be known after one week has elapsed.

**Q3 :** What is the inheritance pattern for the 3<sup>rd</sup> generation?

**A :** Dominant inheritance will continue with a 2 out 4 (50 %) chance of an affected child if only one parent is affected; 75 % chance if both parents are affected. If a child inherited a recessive form of the disease, it is unlikely that his/her children will be affected if the 2<sup>nd</sup> parent does not carry a mutation. Again, screening can only be done if the mutation is known.

**Q4:** How do you explain that a child can have a dominant form of PHHI and that neither parent shows symptoms of PHH?

**A:** An excellent question, and one for which we do not have all the answers. Some individuals with the mutation do have symptoms of hypoglycemia but have never been diagnosed with hyperinsulinism. Some have even had seizures as infants/toddlers but the diagnosis of hyperisnulinism was missed. Others have very mild symptoms or require certain triggers to demonstrate hypoglycemia such as a prolonged fast or a pure protein meal. The spectrum of symptoms, thus, may be a reflection of exposures. Also, other genes may be at work and alter how hyperisnulinism-causing genes work.

## **ARTERIAL STIMULATION WITH VENOUS SAMPLING (ASVS) IN CONGENITAL HYPERINSULINISM**

Robin Kaye, radiologist

Children's Hospital of Philadelphia, Philadelphia, USA

The pancreas is divided into three sections : the head, the body and the tail. Each section is supplied by a separate artery. The gastroduodenal artery (GDA) supplies the head of the pancreas, the superior mesenteric artery (SMA) supplies the body of the pancreas, and the splenic artery (SA) supplies the tail.

The basic procedure of ASVS consists of threading a catheter into each of the arteries supplying the pancreas, injecting calcium to stimulate that section of the pancreas, and then sampling the blood draining from the pancreas to determine insulin levels.. Instead of sampling from small veins that drain the pancreas (as done with the transhepatic venous sampling method), the sampling is done from the hepatic vein.

More precisely, a catheter is inserted via the jugular vein, through the right atrium and almost in straight line through the right hepatic vein. This will be the site for blood sampling during the procedure. A second catheter is inserted through the ? artery. The fact that this artery is close to the surface and is easy to see and feel makes it it the safest artery to use for pancreatic stimulation. From the ? artery, the catheter is probed into the abdominal aorta and to the vessels that directly feed the pancreas. Calcium-glutamate is injected in each area of the pancreas to stimulate insulin secretion, and blood sampling is performed at 30, 60, 90 and 120 seconds post injections. An angiogram of each vessel is performed. A ten minute period is left between each injection. Heparin is used with patients that weigh less than 10 kg in order to diminish risks of clot formations. Clot formation maybe more at risk in babies that weight less than 10 kg because the arteries are small and when the blood flow is slowed down, the blood will clot.

Between July 1998 and February 2003, 153 patients were seen at CHOP with diagnosis of hypoglycemia. Sixty-six of the 153 patients failed medical therapy and required surgery. Forty-one of the 66 patients who failed medical management had focal HI whereas 25 had diffuse HI. The mean age of the patients was about 4 months and their weight about 6,6 kg. No significant difference of age, sex ratio and weight was observed between the diffuse and the focal patients.

Forty of the 41 patients with focal HI underwent ASVS. The procedure was successful in 39 of the cases. In one case, the procedure failed because the catheter could not be probed into the artery. Amongst the 39 patients, correct diagnosed location was performed in twenty-seven of the cases (69 %). In three of the cases, results showed elevated insulin levels in areas of the pancreas not contiguous to one another (equivocal cases). Nine of the cases (23,2 %) did not show response to calcium stimulation making results uninterpretable. No wrong diagnosis was made. All 41 cases underwent surgery. Ninety-three percent are considered cured (totally cured or having controlled hypoglycemia). Seven percent have persistent hypoglycemia.

Nineteen of the 25 patients with diffuse HI underwent ASVS. The procedure was successful in all the cases. Out of the remaining six patients, 2 underwent a transhepatic portal vein sampling

only, 2 had prior positive genetic identification and 2 had positive family history. Amongst the nineteen patients that underwent ASVS, five (26 %) were correctly diagnosed, three showed equivocal results, six were interpretable and five (26 %) were incorrectly diagnosed with a focal lesion. Twenty-four of the twenty-five patients with diffuse HI underwent surgery with an initial 95 % pancreatectomy. Nine required a second pancreatectomy and unfortunately one died prior to surgery and another shortly after surgery.

Statistics of the cases treated in Paris that have undergone transhepatic portal venous sampling show that success rates of diagnosis is very similar to the success rate observed at CHOP. The number of correct and incorrect diagnoses made with ASVS and THPVS are basically the same.

Complications may occur when doing the ASVS. Four out of 58 cases had major complications (arterial thrombosis). They all clinically recovered within 48 to 72 hours post procedure although follow-up showed no change in extent of thrombus. Five cases had minor complications (arterial spasm, fluid overload causing cardiac arrhythmia). None had permanent sequelae.

ASVS is a technically challenging procedure especially because the average age of the patients is low. Special measures are taken to ensure an almost 100 % success rate: Ultrasound guidance for arterial puncture, heparin use for all patients 10 kg or less, no arterial sheath is used (because of increased risk of thrombosis), microcatheters are used to stimulate within the arteries to prevent arterial spasm, and strict attention is paid to fluid and contrast volumes.

Statistical results show that ASVS is successful in pre-operative localization of focal HI. On the other hand, ASVS is not a method for determining focal vs diffuse HI. It can diagnose diffuse HI but it clearly is not the best way. Focal and diffuse HI are completely separate entities. Focal HI can be cured whereas diffuse HI may not be. Diagnosis and treatment of diffuse HI remains very challenging.

## **SURGICAL TREATMENT OF HI**

Scott Adzick, pediatric surgeon

Children's Hospital of Philadelphia, Philadelphia, USA

The surgical approach to resolve focal HI at CHOP is based on the expertise of a multidisciplinary team. The team is made up of four specialists : an endocrinologist (Dr. Stanley), an interventional radiologist (Dr. Kaye), an anesthesiologist (Dr. Litman), a pathologist (Dr. Ruchelli) and a surgeon (Dr. Adzick).

Past reports have shown that the incidence of focal HI varies from a range of 30 to about 50 %. As discussed in previous presentations, recessive mutations cause diffuse HI, whereas loss of heterozygotity together with inheritance of a paternal mutation cause focal HI; the two forms of HI are clinically identical.

The standard approach for patients requiring surgery for congenital hyperinsulinism has been to perform a 95 % or near-total pancreatectomy; this approach is in the midst of change.

The surgical approach at CHOP changed about 4 years ago. If preoperative tests suggest a diffuse type of HI, than biopsies are taken during surgery to confirm diffuse disease and then a near-total pancreatectomy is performed.

If preoperative exams suggest that the HI is due to a focal lesion, intraoperative biopsies are also taken to localize the lesion and a partial pancreatectomy is performed to completely remove the focal lesion. Since focal lesions are usually quite small and basically undistinguishable from the normal pancreatic tissue, the key to this approach lies with the superbly skilled pediatric pathologist who reads the frozen sections and guides the surgeon during the operation. The ASVS performed by our interventional radiologist also helps a great deal in the case of a positive focal lesion because it helps localize the area to be removed. An important part of the procedure is thus spent localizing the lesion. With the expertise acquired, Dr. Adzick has come to identify subtle visual (slightly reddish-brown or marbled appearance,) and tactile (firmer tissue) clues to help find focal lesion intraoperatively. These clues are present in about 66% of cases based on Dr. Adzick's experience.

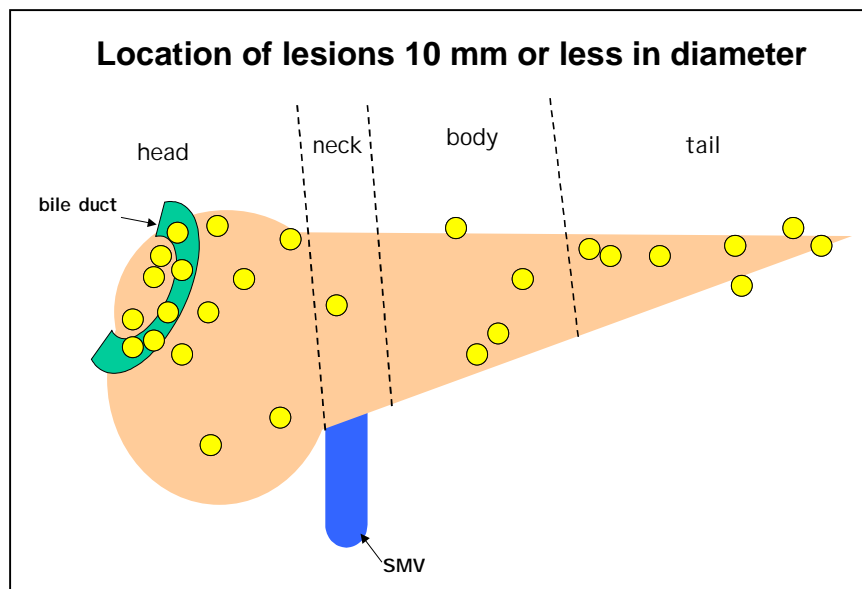
A review of the thirty-eight patients treated for focal HI at CHOP, following the multidisciplinary approach between December 1998 and January 2003, was done in order to evaluate the effectiveness of the radiologic procedure in the localization of focal HI (particularly the calcium angiogram or ASVS) and to assess the clinical outcome of partial pancreatectomy in infants with focal HI. The prevalence of focal HI at CHOP during the four year period was 63 %. The high incidence is most probably due to selection by referral of specific cases to CHOP. Out of 64 pancreatectomy patients, 38 had focal HI, 2 had focal HI with a 95 % pancreatectomy previously done elsewhere (with the focal lesion left in the remaining 5 %), and 24 had the diffuse form.

Just about everything has been tried to localize the focal lesion: ultrasound (preoperative and intraoperative), MRI, CT, PET, contrast angiography and even radio-labelled octreotide scans. All were shown to be ineffective so CHOP has come to use the ASVS with all the pros and cons

of this technique. Out of the 38 patients with focal HI, 36 underwent ASVS (the remaining two patients were too small for successful angiography). In 26 cases (72 % of the 36 candidates for ASVS) the focal lesion was accurately located. Out of six patients who underwent transhepatic portal and splenic venous sampling, only two (33 %) focal lesions were accurately localized.

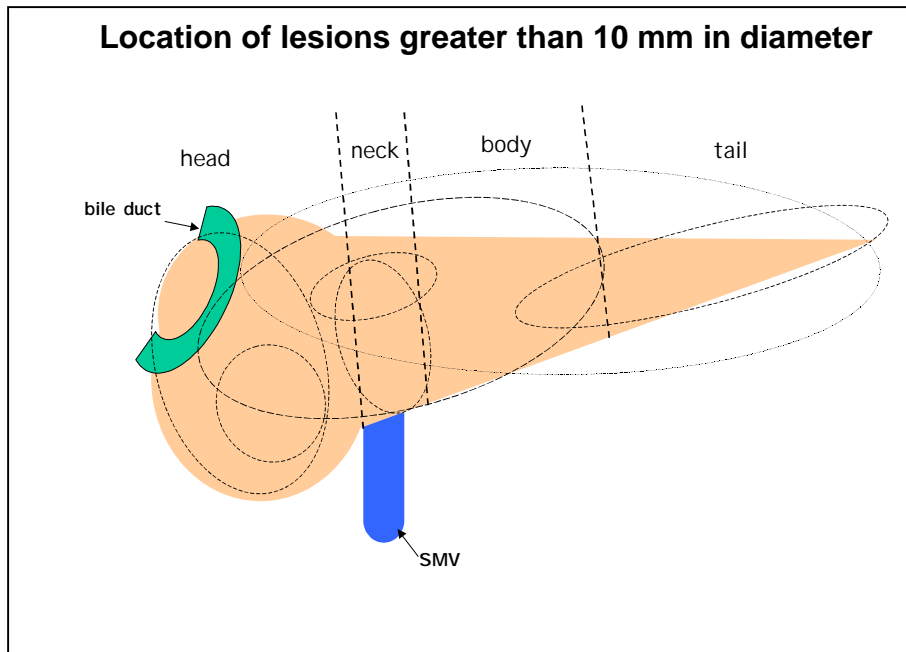
The age at the time of operation of the 38 cases varied from 2 weeks to 14 months with a median age of 10 weeks. Twenty-seven of the focal lesions were 10 mm or less in diameter, eleven lesions were larger than 10 mm and a few were much larger. The extent of the pancreatectomy performed on the 38 cases ranged from 5 to 98 %. The extent of most pancreatectomies (24/38) were 50 % or less.

The diagram below shows the localization of the lesions 10 mm or less in diameter.



Fifteen of the lesions of 10 mm or less in size were localized in the head of the pancreas. This means that with a standard approach (95% distal pancreatectomy) many of the cases would not be cured.

The diagram below shows localization of the lesions having a size greater than 10 mm.



When a large focal lesion is present in the pancreatic head, or when it is uncertain that all the lesion can be removed (a focal lesion often has tentacles that spread out; removal of these is important) a substantial resection of the pancreatic head is performed and a loop of intestine is brought about to anastomose to the remaining normal pancreatic body and tail (pancreaticojejunostomy). This allows us to preserve the normal exocrine and endocrine function of the pancreas.

When the lesions are in the body or tail part of the pancreas, near to the main pancreatic duct (“highway” for all the pancreatic juices and enzymes), a partial distal pancreatectomy is performed.

Thirty-five of the thirty-eight (92 %) focal patients had a complete response to surgery and are cured. Three patients still require glycaemic medication or tube feedings. No patient is a diabetic. The lesson learned from the three cases that still have persistent hypoglycaemia is that the surgical intervention was not aggressive enough. It has been learned that a more accurate intraoperative frozen section confirmation of the clear margins of the focal lesion is imperative. Small pieces of the pancreas are thus taken away until the pathologists confirm that only normal tissue is left.

Surgical complications may occur. Out of the 38 patients, additional resection was needed for three of them for residual disease; two of the three patients were cured. The third patient has persistent hypoglycaemia treated medically despite complete pancreatectomy and

choledochoduodenostomy. It is suspected that there is additional unresected focal lesion within the duodenal wall.

Adhesive small bowel obstruction occurred in two cases, requiring laparotomy and enterolysis. Chylous ascites occurred in three patients, which quickly resolved with elemental formula.

Twenty-four cases of diffuse disease were treated with 95 to 98 % pancreatectomy. One third of the twenty-four cases are well-controlled, one-third are diabetic and the other third required glycaemic medication or a second pancreatectomy (6 cases). Two required choledochoduodenostomy, one required resection of distal duodenum. There was one preoperative death due to necrotizing enterocolitis. One patient died 2-3 years post operation due to sepsis. Near total pancreatectomy implies a long-term risk of insulin-dependent diabetes.

A multidisciplinary approach to congenital hyperinsulinism can distinguish focal from diffuse disease, localize the focal lesions and permit a partial pancreatectomy with cure in most patients with focal HI; diffuse HI is still an unsolved problem. Surgery is not a cure for diffuse HI but needs to be considered to prevent hypoglycaemia and brain damage.

**Q1 – Have you ever seen two focal lesions or is it always rather just one?**

A – We have seen some atypical pathologies that we are still trying to sort out but never two distinct focal lesions of less than 10 mm in size.

**Q2 – What is choledochoduodenostomy?**

A – Anastomosis of the common bile duct to the duodenum.

**Q3 – You mention that surgery is not a cure for the diffuse type, but it is also mentioned that only 50 % of the diffuse patients who had surgery become diabetic; does that mean that the other 50 % were cured?**

A (Dr. Thornton) – Sometimes, after a partial pancreatectomy, one can take enough pancreas out and get a fine balance between not too much and enough insulin secretion to secure a overnight fast. But if these children fasted for a longer period of time they would go low. They are practically in remission, having no lows on a normal eating pattern, but if vomiting were to occur or if access to food was not possible, they would go low.

**Q4 – Is intestinal hernia following a pancreatectomy a common occurrence?**

A- No.

## **NON-SURGICAL TREATMENT OF SEVERE HYPERINSULINISM AND ITS LONG TERM OUTCOME**

David Gillis, paediatric endocrinologist

Hadassah Hebrew University Medical Center, Ein-kerem, Jerusalem, Israel

Treatment of hyperinsulinism (HI) in our institution tends towards non-surgical treatment whenever possible and this will be the focus of my talk. However, before talking about treatment, it is important to understand what HI is and also what it is not. HI is a condition in which the secretion of insulin is dysregulated. As a result, glucose levels are often very low, but can occasionally also become very high because of an unsatisfactory insulin response to glucose. One might say that both the "on switch" and the "off switch" do not work when and how they are supposed to. As explained in previous presentations, this problem can be caused in different patients by mutations in several genes, with some variation in the clinical presentation depending, in part, on the particular gene involved.

The major concern is hypoglycemia which may be noted in the immediate neonatal period or later on in infancy. Most patients with the severe form are treated with pancreatectomy with or without additional medication. In our center we have pioneered an aggressive non-surgical approach which I will explain in further detail later. We have found that after years of careful medical treatment patients tend to have fewer episodes of hypoglycaemia and go into what we term "remission". On the other hand, after surgery many patients develop diabetes although, as mentioned by Dr. Stanley, it is often a mild form unless near total pancreatectomy is performed.

HI is not a malignancy, it doesn't grow or spread. It's previous name; nesidioblastosis, was given because it was thought that it had to do with sprouting of the pancreatic Beta-cells. Histology studies later showed that HI tissue resembles the newborn normal pancreatic tissue. HI doesn't seem to be a disease that gets worse with time. In most cases, it is not associated with clinical diabetes unless pancreatectomy is performed.

So why do we need to take out the pancreas? This is not a simple question to answer. The main idea is to prevent hypoglycemia and damage to the brain. So if one can avoid hypoglycemia otherwise, we can prevent damage to the brain with other methods.

Even if one can avoid hypoglycemia, managing the patient is no simple matter when the surgical approach is not taken. So the idea is to make the patient more manageable not only for his/her benefit but also to prevent "damage" to the family. The stress of non-surgical treatment is tremendous. We are talking about staying up at night for many years, and making every effort to follow the intense regimen of feeding and medication. This responsibility and task most usually rests on the mother. Some parents are ready to handle such a situation in order to avoid the diabetes that would result from pancreatectomy, but clearly it is not an option for every family. Also, in some cases, maximum conservative therapy cannot prevent hypoglycaemia and surgery is the only way to go.

So why should we not take the pancreas out? The main reason for avoiding surgery is the natural history of the disease. As I have already mentioned, after a period of time with intensive non-

surgical treatment, the disease will eventually remit. Hypoglycemia become less severe and more manageable, and patients become better in general. Aside from that, pancreatectomy is major surgery which has possible complications. If it can be avoided, it is all the best. The major long-term advantage of the non-surgical approach is the avoidance of diabetes.

So, how do we go about non-surgical management ? In order to simplify things I think it is best to look at the process as one including several major steps:

- 1) HI is diagnosed, based on a requirement for high glucose intake, and biochemical evidence of inappropriately high insulin levels. In populations with known mutations, genetic testing can facilitate the diagnosis.
- 2) Following diagnosis, and even prior to it, glucose is given intravenously through a central venous catheter at high doses. In parallel with the glucose or infusion, oral diazoxide is tried.
- 3) Weaning of glucose infusion is attempted in order to assess the effectiveness of diazoxide.
- 4) If the diazoxide is proven to be ineffective, the procedure is started over again with octreotide. The dose of octreotide must not go beyond 15-20 µg/kg/day. Beyond this dose, octreotide will not only decrease insulin production but also glucagon. If maximum doses of octreotide are unsuccessful, glucagon infusion is added.

The very intensive intravenous therapy with octreotide and glucagon is not without difficulty. It demands prolonged hospitalisation (several weeks to months) and may cause GI problems.

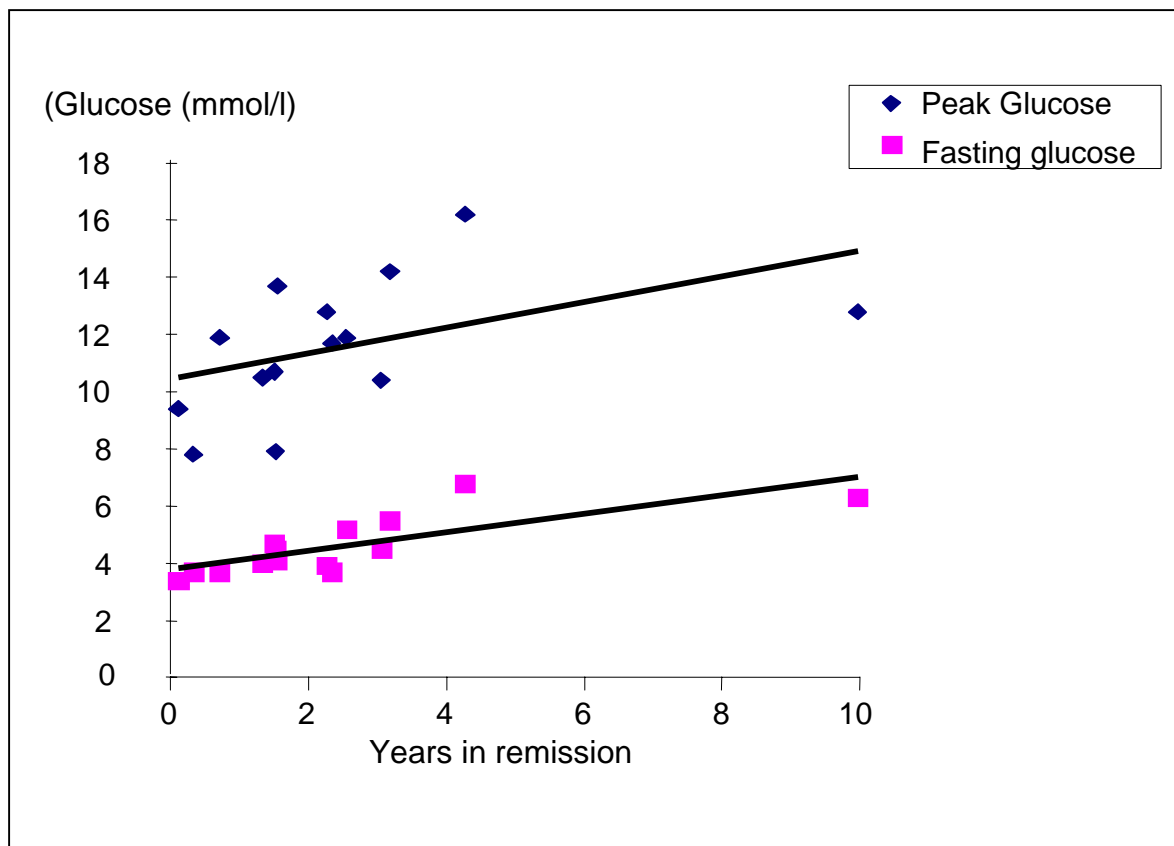
- 5) Over time, one can gradually wean the patient from intravenous management, gradually stopping drugs and intravenous fluids. At this stage the patient is usually given continuous feeding. Gastrostomy is performed at this stage to permit continuous feeding.
- 6) Intravenous octreotide can be changed to subcutaneous injections. Patients can be discharged with 4 to 6 injections a day or continuous octreotide pump therapy.
- 7) Once the intravenous therapy is stopped, we can start thinking about sending the child home.
- 8) Eventually, from continuous feedings, the patient can go to bolus feedings with increasing proportions of the food given by mouth.

HI remission may be in part explained by the natural process observed in all types of body cells which defines programmed death (apoptosis). This natural process plays an important role in preventing appearance of tumours. Several papers show that this natural process seems to happen more intensely in the pancreas of HI patients (based on data from surgical specimens). Perhaps the octreotide itself may increase or induce apoptosis.

Statistics for long term follow-up of eighteen patients with SUR1 mutations treated with medication and intensive non-surgical management at Hadassah are as follows. Twelve of the cases were homozygous whereas 6 had the paternal mutation (heterozygous). Thirteen (8 homozygous, 5 heterozygous) are currently in remission. Average age of remission of homozygous cases is higher ( $6.8 \pm 1.6$  yrs) than in heterozygous patients ( $3.1 \pm 2.8$ ).

A patient is said to be in remission when he has the capability to fast overnight and when he/she does not need frequent feedings, medication or cornstarch to maintain glucose levels.

Long term study of the peak values of insulin and glucose after oral glucose challenge shows a gradual increase in both, probably due to puberty (Figure 1). The patients with paternal mutations only, have significantly higher peak levels of insulin (see box within figure 2). After a challenge with a standard meal, surprisingly, the peak glucose levels are lower, but the peak insulin levels are higher compared with oral glucose challenge (depicted as OGTT in the figure) (figure 3) . In an example from a particularly compliant patient followed with repeated oral glucose challenge testing for several years, it appears that with time the response to oral glucose worsens although the glucose after a standard meal remains fine (figure 4). No patient treated conservatively has an elevated Hemoglobin A1c, meaning that no patient has an abnormal 3 month average glucose



**Figure 1: Oral glucose tolerance test results with time in remission**

Note: The text that follows reflects the opinion of the author only

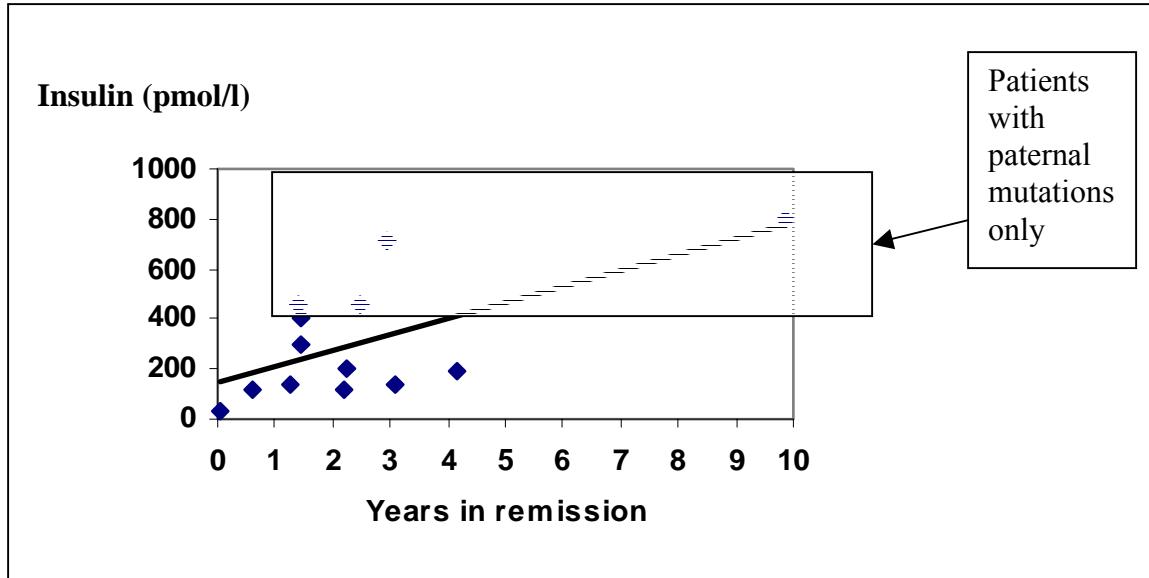


Figure 2: Peak insulin with time in remission

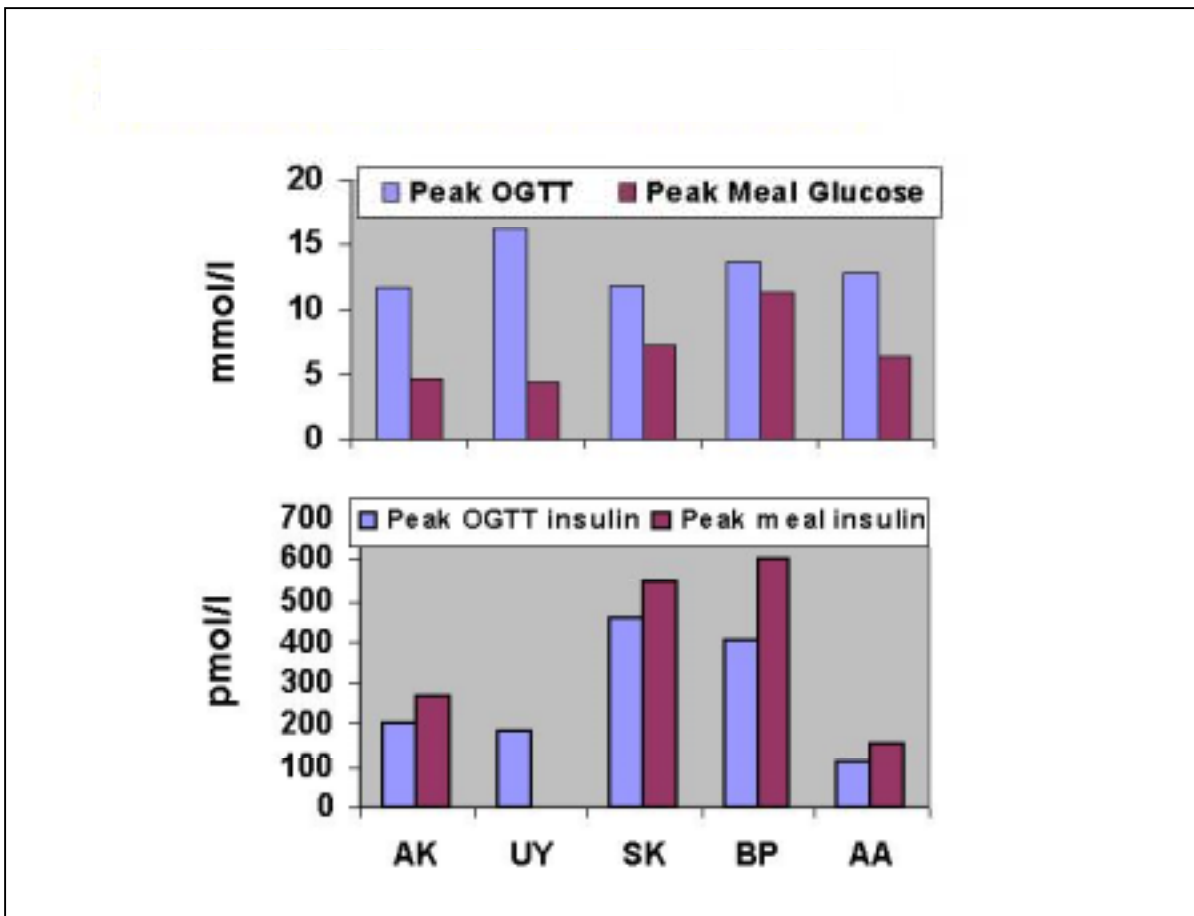


Figure 3: Insulin and glucose, meal and oral glucose tolerance test

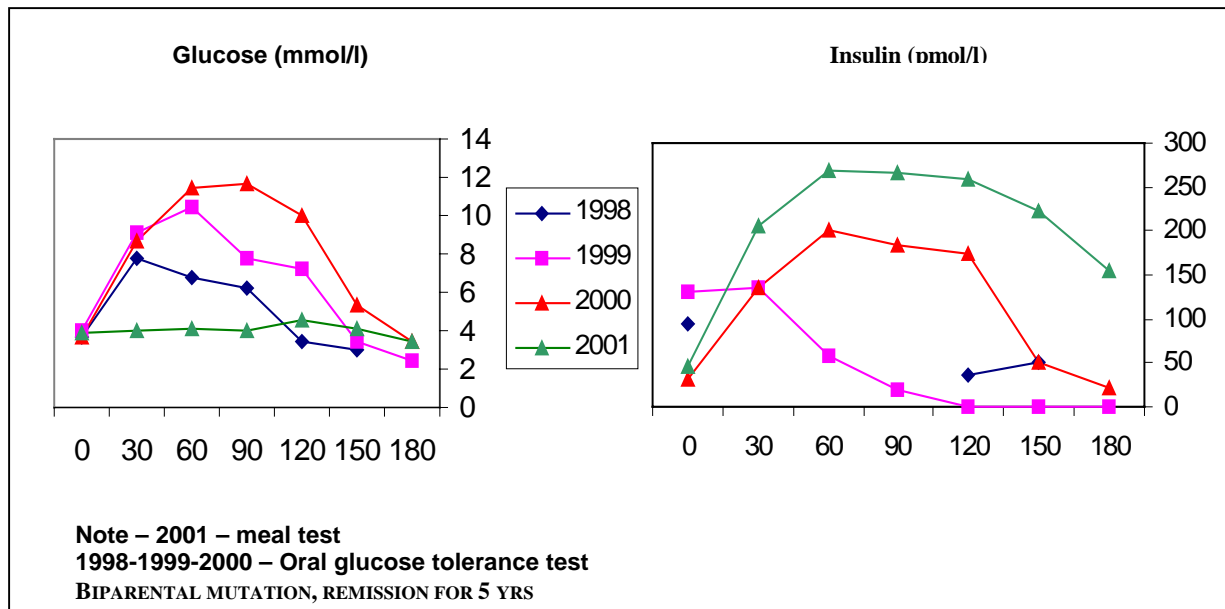


Figure 4: Long term study of the peak values of insulin and glucose after oral glucose challenge – repeated testing in patient over 4 years.

In summary, the conservative approach in diazoxide-non-responsive patients can be accomplished by very intensive management with a combination of feeding, octreotide and glucagon. It appears that patients treated appropriately in this way are not neurologically impaired and do not develop diabetes.

**Q1: How do you define severe HI?**

A: HI is considered severe when there are constant low BSIs, when there is no, or very minor response to diazoxide and a high need of IV glucose.

**Q2: At what age do you see remission in children treated with diazoxide?**

A: If the patient has HI/HA there seems to be no remission, although these children are sensitive to diazoxide and therefore are managed non-surgically in all centers to the best of my knowledge. In patients with SUR1 the timing of spontaneous remission differs between the homozygous and heterozygous (paternal mutation) forms, with earlier remission in the heterozygous group. I mentioned the actual ages from our small series in my lecture.

**Q3: In Israel, premarital testing is done and arranged marriages are performed in order to avoid several types of disease. Will HI be added to the list of detected disease?**

A: This is a matter that we are currently discussing with the group which performs premarital screening "dor yesharim". Since there are relatively few common mutations this possibility exists. One must remember however, that arranged marriages are common in only a small

*Note: The text that follows reflects the opinion of the author only*

part of Israeli society (the ultra-orthodox), but perhaps fortunately, this particular segment of society is more prone to HI. So the answer to your question is "probably in the near future".

## **Diagnosis and management of HI: The approach at Great Ormond Street Children's Hospital, London UK**

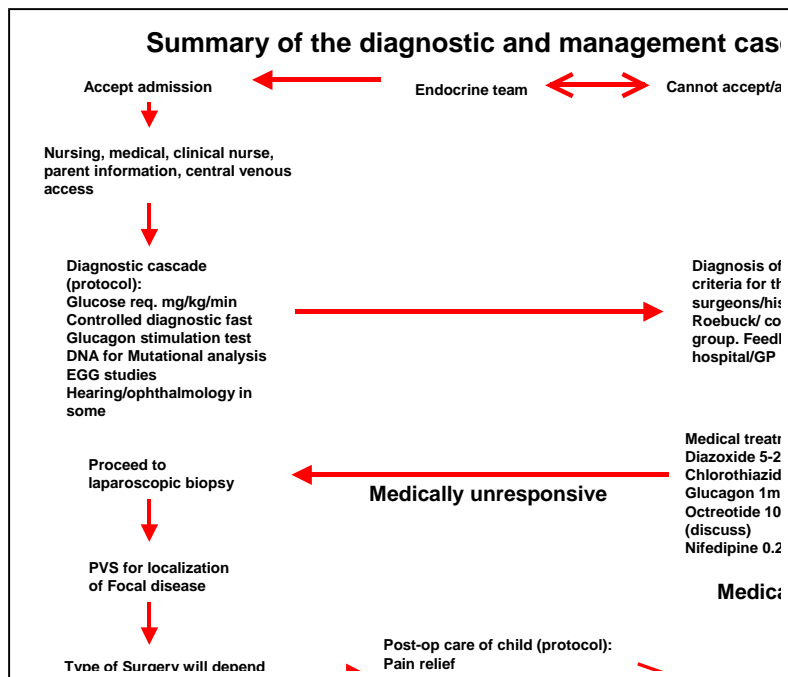
Khalid Hussain, paediatric endocrinologist  
Great Ormond Street Hospital, London, UK

The London Center for childhood pancreatic disease (LCCPD) is a national and international referral center for HI. An average 15-20 new patients are received each year, about 10-15 of which are from the United Kingdom. The LCCPD team works in close collaboration with the referring teams and protocols are in place for the stabilization and safe transfer of patients to Great Ormond Street Children's Hospital.

Hyperinsulinism generates some of the most formidable practical problems in contemporary paediatric endocrinology. It should only be managed in centers experienced in the totality of care needed. New approaches to diagnosis and management are being developed and research is providing a unique understanding of the normal physiological mechanisms regulating insulin secretion.

The practical management of HI is a real challenge! The aim is to keep blood glucose concentrations between 3 and 10 mmol/l (54 and 180 mg/dL). The management of HI is complex as there are always problems that are unrelated to hypoglycaemia or hyperglycaemia. Numerous neonatal complications can also arise like fluid balance problems, cardiac failure, sepsis, line infection, line dislodgement, polycythamia, etc...

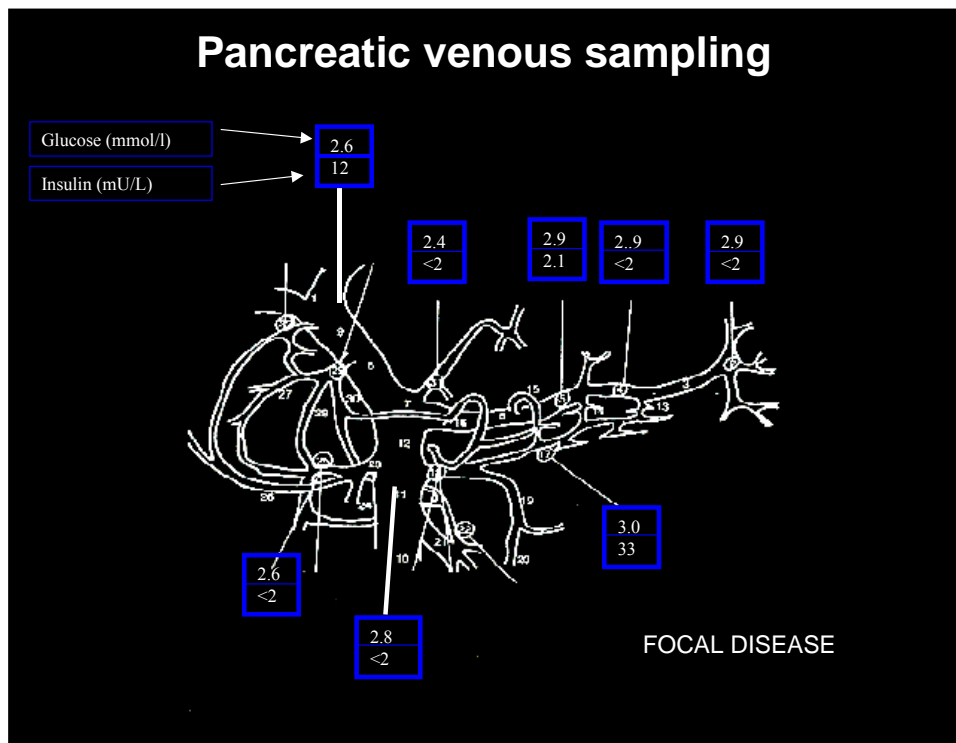
The diagram below is a summary of the procedures followed for diagnosis and management of HI.



Two categories of PHHI exist: the diffuse disease and the focal disease. One of the tools used to identify the histological type of PHHI is the laparoscopic biopsy of the pancreas. Results of the study are known within 24 to 48 hours. If the cells of the pancreas have a large nuclei, it is the diffuse type. If the nuclei are small then it is the focal type. If a focal type is diagnosed, a percutaneous transhepatic pancreatic vein catheterization (PVS) is performed in order to localize the focal lesion<sup>1</sup>.

Performing a pancreatic venous sampling demands meticulous preparation. It is a technically difficult and challenging procedure. The patients blood glucose levels need to be between 2,6 and 3 mmol/l (46,8 and 54 mg/dL) during the intervention. The goal of the intervention is to identify “hot spot” of insulin secretion. Interpretation of the results is difficult and sometimes impossible. Because of the difficulty of canulating very tiny venules sometimes the focal lesion cannot be detected.

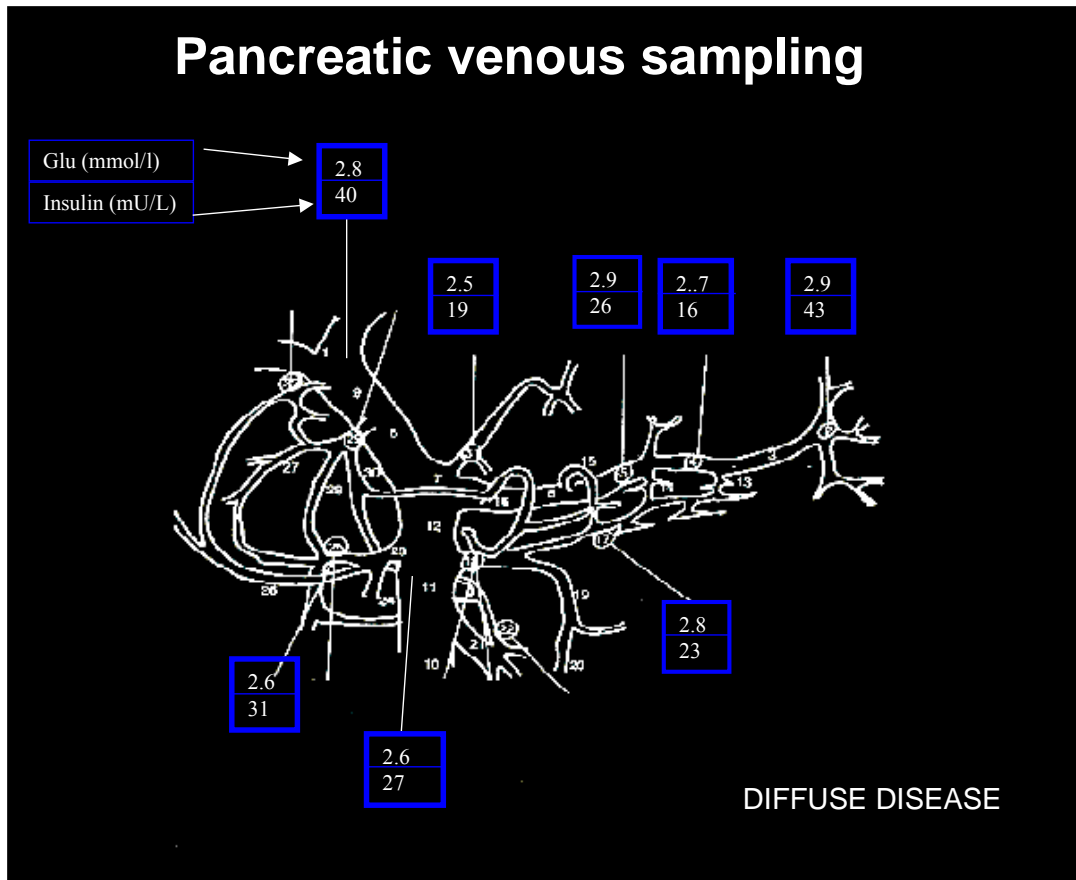
The diagrams below shows an example of insulin secretion in relation with blood glucose level for a focal type of PHHI as measured during a PVS.



<sup>1</sup> 2004 update: The advances in PHHI are proceeding at such a pace that we no longer do PVS, but now perform a special investigation called a PET scan to localize the focal lesion. The reason for not doing the PVS anymore is because the PET scan seems to be more sensitive in picking up those children with the focal lesions and less invasive than PVS. This is a decision we have adopted in our unit, I cannot speak for other units.

*Note: The text that follows reflects the opinion of the author only*

The diagrams below shows an example of insulin secretion in relation with blood glucose level for a focal type of PHHI as measured during a PVS.



Dr. Hussain finishes his lecture by presenting the European Network for Research into Hyperinsulinism (ENRHI). The ENRHI was initiated in 1995 by an international partnership. It involves 14 countries and links 40 clinical investigators and basic scientists. It holds regular scientific workshops. Over 40 publications, generating new insights, are issued from the ENRHI.

## **HYPOGLYCEMIA, BRAIN INJURY AND DEVELOPMENTAL CONSEQUENCES**

Lawrence W. Brown, paediatric neurologist  
Children's Hospital of Philadelphia, Philadelphia, USA

Dr. Brown begins his presentation by paying tribute to Lester Baker.

The goal of Dr. Brown's presentation is to present the neurologist's perspective on hypersinsulinism: to explain the importance of blood sugar and why hypoglycemia can lead to brain injury.

Glucose is the primary fuel for the brain, although our body can switch energy sources to use ketones (fats) under periods of starvation. Glucose for the brain is derived from the blood. The relatively large size and rapid growth of the brain in newborns (and especially in premature infants) makes the brain's metabolic demands to be the major determinant of hepatic glucose productions. Glucose crosses the blood brain barrier through glucose transporters that facilitate glucose uptake (and keeps other things out of the brain cells) in addition to passive diffusion. Brain glucose not only offers a source for energy, but also plays an active role in brain development by providing substrate for synthesis of amino acids and lipids in the immature brain.

Blood sugar drops very rapidly following the first hours of life in normal newborns. The infant can no longer rely on placental supply, but rather is forced to provide his or her own energy sources. Despite this, glucose levels generally stay within the range of 60 to 80 mg/dl (3.3 to 4.4 mmol/l). Lower glucose levels are occasionally reported, but generally there are no symptoms unless the levels fall significantly below that level.

In addition to the role of glucose as the primary source for energy, it functions as an important source for production of other important structural and metabolic derivatives including:

- ◆ nucleic acids, which are important for protection against damage;
- ◆ amino acids, which are the building blocks of protein;
- ◆ ketone bodies, which are an alternate source of fuel for the brain;
- ◆ acetylcholine which is a major neurotransmitter.

The neurologist's definition of hypoglycemia is when the blood glucose level is below the critical limit for maintenance of metabolic homeostasis and neural integrity. The critical blood glucose level is usually defined as any level below 30 mg/dl (1.6 mmol/l) in term infants and below 20 mg/dl (1.1 mmol/l) in prematures. But there is evidence of potential injury if recurrent glucose levels below 45 mg/dl (2.5 mmol/l) are observed. Also, critical values for brain injury from hypoglycemia can occur at higher blood sugar levels in the presence of co-existing asphyxia, infection, or other stresses. Clinical signs of hypoglycemia in neonates can be extremely subtle (from duskiess to constipation to low temperature); this may make it extremely difficult for the neonatologist to identify hypoglycemia as a problem.

Symptoms of hypoglycemia in infancy include:

- ◆ high pitched abnormal cry
- ◆ apnea, cyanosis
- ◆ feeding difficulties
- ◆ tachypnea, grunting
- ◆ hypothermia
- ◆ hypotonia, limpness
- ◆ somnolence
- ◆ irritability
- ◆ jitteriness, tremors
- ◆ lethargy, stupor
- ◆ tachycardia
- ◆ sweating
- ◆ seizures

The most important sign of neurological injury is the presence of seizures.

As mentioned above, glucose is actively transported into the brain by glucose transporters. The glucose transporters become rate limiting at 45 mg/dl (2.5 mmol/l). Once liver glycogen is depleted, blood glucose comes from mobilization of amino acids (protein) and free fatty acids. Breakdown of protein and fat can also occur within the brain, thus further contributing to potential injury.

In the presence of early hypoglycemia, the brain reacts to compensate for the low levels of blood glucose. Glycogenolysis (glycogen breakdown) is increased, cerebral metabolic rate decreases to lower brain glucose requirements, and oxygen utilization also decreases. The brain starts looking for alternate energy substrates; amino acids are consumed while lactate, ketones and ammonia levels. If the cerebral blood flow can keep up and compensate for the low blood glucose levels, no biochemical effects will be noticed and no long term problems will occur. However, the brain will suffer if hypoglycemia persists and alternate energy substrates are no longer available. Breakdown of structural components begin to happen as the brain tries to keep up with its energy needs. That is when energy failure leads to coma and brain death.

Fortunately, neonates are more resistant to hypoglycemia than the older child and adult. This can be explained by lower cerebral energy utilization, increased cerebral blood flow even with moderate hypoglycemia, higher cerebral utilization and uptake of lactate, and increased resistance of the neonatal heart to hypoglycemia. Fortunately, even severe cases of hypoglycemia often resolve without neurological injury, due to our body's flexibility and resilience. It must be mentioned that brain hemorrhage is more common as a consequence of hypoglycemia in premature newborns due to increased cerebral blood flow damaging an immature blood vessel network.

Neonatal hypoglycemia is more likely to have poor outcome in the presence of:

- ♦ encephalopathy
- ♦ prolonged duration of hypoglycemia
- ♦ seizures
- ♦ associated central nervous system insults including asphyxia and other birth injuries.

Case studies of infants with any cause for severe hypoglycemia (not only HI) demonstrate that the prognosis of normal neurological outcome is worse if there are neurological abnormalities (floppiness, apnea, jitteriness) and becomes even more severe in the presence of seizures. Only 38% of infants with hypoglycemia have a normal outcome if their presentation included neurological abnormalities and seizures. Observed neurological abnormalities usually last weeks, sometimes months, but often resolve with time. Unfortunately, this particular study did not address milder neurodevelopmental problems such as learning disabilities or behavioral problems as affected children were not followed until school age.

during a seizure

Duration of hypoglycemia is another important prognostic indicator. Adverse outcomes including cerebral palsy, mental retardation, autism, epilepsy and other major developmental disabilities increase with the duration of hypoglycemia. One study showed a strong increase in poor neurological outcome from 29 to 40 % when there was at least one value below 47 mg/dl (2.6 mmol/l) observed daily over more than 3 to 7 days.

Mortality from untreated hypoglycemia is now rare, but development disabilities are still extremely common. Morbidity includes MR, cerebral palsy (spasticity, ataxia), epilepsy, and acquired microcephaly. The single most important factor in preventing these adverse outcomes is how quickly treatment is initiated.

Hypoglycemia is not the most common cause of neonatal seizure but it one of the most important treatable causes. A seizure requires energy as it is a rapid and repetitive activity of large neural networks in the brain. Brain glucose utilization during a seizure is increased by 200 to 500 %. Even in the presence of normal blood glucose a rapid decrease in brain glucose is observed despite efforts to compensate. But it is more likely for hypoglycemia as the etiology of seizures to cause brain injury, since there is a double challenge of keeping up with the markedly increased metabolic demand when the major energy substrate is lacking. Anaerobic metabolism (from anoxia or ischemia) leads to build up of brain lactate which can be a further brain injury factor. In the absence of hypoglycemia, a prolonged seizure (usually beyond 60 minutes) will begin to produce central hypoglycemia causing cerebral failure; this occurs quicker under conditions of hypoglycemia.

An experimental model by Vannucci showed that hypoxia (lack of oxygen) combined with hypoglycemia causes death in the experimental animal more rapidly. Normoglycemic animals can compensate for hypoglycemia by anaerobic metabolism but hypoglycemic animals do not increase glycolytic intermediate thus causing energy failure.

There is relatively little known about the outcome of severe hypoglycemia of infancy. One interesting retrospective study reviewed the results in a large group of children originally diagnosed with hyperinsulinism in infancy and early childhood. Out of the 54 neonates, few were medically treated only (8 of 46) while the majority underwent surgical procedures for focal adenomatous hyperplasia or diffuse hyperinsulinism. When hypoglycemia presented later in infancy, more than half (19 of 36) were successfully managed by medical treatment while the remainder underwent pancreatectomy for focal adenomatous hyperplasia or diffuse hyperinsulinism. Patients were studied at baseline, 3 and 10 years old. Intellectual outcome, academic achievement behavior disorders, neurological disorders and needs of supportive services were noted. In general, prognosis was better when hypoglycemia presented later in infancy and when the problem could be successfully managed medically without need for surgery. The presence of seizures, presumably as a marker of the severity of brain injury, was the most important adverse predictor of significant disability. Poor outcome was even more likely if seizures were combined with microcephaly (failure of expected brain growth). These findings were confirmed in a very recent review of 68 patients treated here at CHOP. In this telephone survey approximately half were medically controlled and half had undergone surgery. Most children had good outcome, but the curve was shifted downward; the surgery group fared worse. As in the other study, onset in the first week of life was associated with increased disability and the need for special education.

**Q1:** My child has ADHD; what is the relationship to his hypoglycemia in infancy?

**A:** ADHD is usually an independent issue, since it almost always occurs in the absence of hypoglycemia. But it is reasonable to assume that the extra metabolic stress from hypoglycemia contributed to the development of ADHD.

**Q2:** What are the characteristics of periventricular leukomalacia?

**A:** Periventricular leukomalacia (PVL) is a white matter injury caused by a lack of blood flow to the vulnerable immature brain of premature infants. This area is the last to be perfused, so any inadequate blood flow can lead to damage before other regions. Common causes include low blood sugar – but also high blood pressure, low blood pressure, toxic effects of meningitis... The premature brain is most at risk because this region has a high metabolic rate as well as immature blood vessel network, in addition to the fact that it is at the end of the stream. PVL affects the white matter which is the system of cables connecting the nerve cells of the cortex to the rest of the nervous system. Whereas injuries to the cortex (grey matter) will lead to retardation and seizures, injuries to the white matter result in tightness or spasticity.

**Q3:** What is the time lapse necessary for hypoglycemia to result in brain damage

**A:** We don't completely know how short a period of hypoglycemia is necessary to produce brain injury. Likely, it can occur within minutes in a vulnerable newborn. An asymptomatic child over a year of age, can definitely handle hypoglycemic stress much better. They present much differently with much earlier signs like excessive sweat, jitteriness, headaches... And they are more protected against brain damage even when they have seizures; it usually takes one to two hours of seizure before injury will result.

(Dr. Stanley agrees that we do not know how long it takes before brain injury occurs.)  
Not all prolonged seizures lead to injury. Most seizures stop on their own within 5 minutes. Status epilepticus is a state of persistent seizures and is usually defined operationally as one seizure lasting 20-30 minutes, or recurrent seizures of that duration without full recovery of awareness between seizures. Beyond that point it becomes increasingly unlikely to stop on its own without intervention. Therefore, the take home message is that it is easier to stop the seizure earlier you treat it. So most medical teams will use Diastat (rectal Valium) within 5 to 10 minutes.

**Q4:** If a child suffers sugars low enough to cause brain damage, can he or she recover without medical intervention?

**A:** This is a loaded question with several possible answers. Let's say that an infant has suffered brain damage from undiagnosed hypoglycemia. Certainly, there is hope for eventual recovery, but medical intervention is still necessary to prevent additional stress or damage from further episodes of hypoglycemia, seizures, etc. There are limited data to support the belief that medical intervention or rehabilitation services will reverse brain damage. Still, it is critically important to provide the optimal environment for recovery and growth including good nutrition, prevention of orthopedic deformities, physical therapy, and a stimulating environment.

## **FEEDING ISSUES IN CHILDREN WITH HI**

Maria Ramsay, Ph.D psychologist

Montreal children's hospital and McGill University, Quebec, Canada

Feeding problems can be observed in children with medical problems but also in children that are otherwise healthy. In the 1980's it was believed that if a child would not eat it was because the mother did something wrong (didn't offer the proper food, or offered it the wrong way or at the wrong time...). This theory has evolved into thinking that feeding is a complex phenomenon that also involves the physiology of the child. In this presentation the normal feeding pattern, including feeding as a developmental skill, feeding as a physiological process, feeding as a visceral learning and feeding as a social act will be looked into, from several aspects.

### *Feeding as a developmental skill*

The first aspect to look at in a normal feeding pattern is how the feeding skill develops. The newborn is born with reflexive sucking which disappears around the age of 2 to 3 months. At the same time, the sucking pads in the mouth, which aid the newborn to suck while the muscle tone is not yet developed, reabsorb. This explains that some children with no medical problems, that grow well for the first 3 months have been seen to suddenly eat less adequately at 3½ months. At 3 to 4 months tongue protrusion diminishes. Tongue lateralization, happening at about 6 months is very important in bringing about jaw lateralization which is very important in the ability to tolerate textured food.

Feeding skills fit in very beautifully with other developmental skills like speech, fine and gross motor skills. The same way we can understand that a child will not walk before it learns to stand; we can understand that a child will not learn to chew before it learns to munch.

Feeding is a highly complex sensori-motor process that will be affected if there has been any neurological insult. Feeding follows a developmental progression, just like any other developmental skill. Also, feeding is dependent on the integrity of the cardio-respiratory and gastrointestinal systems and a variety of hormonal balances.

### *Feeding as a physiological process*

For feeding to take place, appetite needs to be present. If there is desire to eat, the second physiological process taking place will be ingestion of food which includes the sensory system (taste, texture, smell) and motor activity (sucking, chewing).

Very little is known about appetite. It is assumed that every child is born with enough appetite to survive. But that is not entirely true. Even among children that have no medical problem, there are few who don't feel hunger (they never cry for food). It should be no surprise that appetite is a variable as any other physiological process. Appetite is influenced by many factors, among them by taste and gastric motility. The taste of food can increase or decrease appetite. If a taste is not desirable, appetite can decrease. Appetite will also be affected by esophageal or gastric motility

problems. It has been shown that children who have slow emptying of the stomach will not eat according to a normal pattern. Hormones also play a role in appetite. Ghrelin, one of the many hormones regulating initiation and termination of eating, has recently been identified (1999). Until now very few studies have been done with ghrelin in children. However, we know that it is secreted in the stomach and that it acts on the hypothalamus to regulate appetite.

Sucking, chewing and swallowing are ingestive behaviors. The oro/pharyngeal sensory system influences ingestive behavior. If a child can not feel the food in his mouth, it won't eat. Oro/pharyngeal motor skills need to develop in order to have a normal ingestive behavior. Drinking from a bottle implies sucking, swallowing and breathing in a complex coordination pattern. Chewing on the other hand, depends on the development of good tongue lateralization.

Feeding also refers to a visceral learning. An association between two internal events becomes a memory that plays a role in the feeding pattern. For example, the taste of a certain food that causes pain in the stomach will eventually result in the child not wanting to eat that specific food (taste).

The social aspects surrounding eating are just as important in the outcome of the feeding behavior as all other notions discussed above. If feeding times are difficult, the mother and child interaction during feeding becomes distressing for both and eventually the child will learn to avoid eating.

### *Feeding difficulties*

Different feeding difficulties exist. Poor or variable appetite, poor oral-motor coordination, sensory hypersensitivity or hyposensitivity are examples of problems that can develop a distressed behavior pattern. If oral feeding is associated with a feeding difficulty (disorganized sucking, gagging on textures, long mealtimes) a negative conditioning is taking place which will result in an avoidance to eat. The sequence below explains how:

Baby (bb) with small appetite: cries softly → Mother (M) picks up bb → bb turns to nipple → M gives → bb sucks slowly for 2-3 min. and stops → M tries stimulating bb's lips → bb sucks 2-3 times, stops → M does not understand, tries again → bb turns head away → M knows baby needs more milk, worries, tries again → bb arches and cries → M calms bb → bb falls asleep → but wakens soon → same cycle over and over again →→→ both M and bb anticipate struggle (memory), unpleasant feeding periods → eventually feedings become stress ridden.
--

When this type of pattern occurs, the starting point (lack of appetite) very often goes unnoticed and the blame for the difficult feeding behavior is put on something else (mother's impatience, lazy baby,...).

Tube feeding can develop in an oral aversion: The following sequences explains how:

Tube feeding → lack of hunger → unpleasant experience when food in mouth → negative visceral conditioning → refusal → lack of food in mouth → lack of sensorial experience → oral aversion.

HI can lead to specific feeding difficulties. The need to feed every 4 hours to prevent hypoglycemia can bring along a lack of appetite. Also, neurological sequel of the illness can bring along oral motor delays and sensory abnormalities. Many types of medication decrease appetite (like ritalin). Effect of PHHI related medications on appetite has not been documented.

A very important social context develops around feeding difficulties. A sense of guilt and isolation can arise because the family and friends do not understand why the child will not eat.

### *Management of mealtime stresses*

In order to live through difficult feeding periods, parents need to understand feeding and learned behaviors. Know that appetite is variable and that in a child with PHHI can be affected by both the illness and the treatment.

Self-nurturing and support by family and friends are very important. Stressed parents are more likely to increase mealtime struggles. Parents need to learn to leave their child with friends and family regularly, even for short periods of time, before 6 months of age to reduce over-attachment later. The child needs to learn that people other than its parents can take care of it.

Early involvement of an occupation therapist for oral exercises are important to maintain stimulation of the oral sphere. Oral stimulation during tube feeding in order to associate pleasurable sensation near mouth can help. Use music and gentle stroking initially at ears, or on forehead, nose, then around the lips, to help connections between stomach distention and pleasurable sensation near mouth. When the baby is ready to accept some food in mouth, work with tastes, not amounts. At a later age, put tiny amounts on plate, praise for finishing plate. Success is a pleasurable feeling and gives the child a sense of mastery. Next time the child will expect success.

Manage feeding behavior by ignoring disruptive and non-feeding acts and praising positive feeding-related behaviors. For example: find a moment of positive behavior in the midst of a negative behaviors and start praising it (baby shaking head as she looks at the spoon. Mom says: Oh, you looked at the spoon, good girl!). Find external interest to motivate eating (special TV program, drawing, special games). Start with 1-2 spoonfuls (very small goals) to give reward. Avoid making negative comments or threats. Instead of saying “you can't have this until ...” say “you can have this when...”

No medication is specifically designed to increase appetite but side effects of some medication may help. Periactin (cyproheptadine) is an antihistamine that has been shown to increase appetite and so has the hormone Megace (megestrol acetate).

Prognosis of feeding impairment in PHHI children depends on the severity of HI, the severity of neurological involvement, the timing of intervention, the use of medication and family circumstances.

Q1: How would you explain the origin of feeding issues in children with PHHI?

**A:** From birth on children respond to both internal and external experiences in shaping their feeding behaviors. The hunger cry in the newborn is the first signal of internal cue to feed. If for reasons of low appetite, weak sucking ability or low sensitivity to taste the infant does not feed adequate amounts, the external world (the mother) will respond with increased efforts at trying to get the infant feed more. This start to alter the feeding experience and eventually may become a feeding problem. Illnesses, gastric motility and medications further influence the feeding problem. It is possible that feeding started off well at birth and later, due to significant psychosocial problems, the child learns to avoid eating, but this type of feeding problem is in my opinion relatively rare.

# Join our discussion and support group

Families living with PHHI  
are among those who have  
greatly derived benefit from the expansion of internet

To this day, the YAHOO HYPERINS discussion group  
has brought together more than 100 families.

Over 12 000 messages are archived on the site  
containing a variety of information about how we live with PHHI.

But mainly, our group is there for support,  
as a forum for open and honest exchange of ideas  
and simply to create a feeling of togetherness often needed  
by all families who live with this rare disease that is PHHI.

So whether you are seeking specific information,  
want to share your story,  
or just want to feel part of a big family,  
you are welcome to our group!

Sign in through

<http://health.groups.yahoo.com/group/hyperins/>

Note that different PHHI yahoo groups have been created to facilitate exchange between  
members of different speaking languages.

Those who prefer to communicate in Spanish will find the Spanish group at

<http://es.groups.yahoo.com/group/hiper/>

Also visit our website at

[www.surl.org](http://www.surl.org)

for all links to those groups and much more!

# Histories

Faces of Congenital HyperInsulinism  
A twenty-minute film

Congenital Hyperinsulinism (HI) is a rare genetic disease causing severe hypoglycemia. If left untreated HI can lead to brain damage. Early treatment and proper daily management reduce that risk. At the first international family conference on this disorder, HI family members and their physicians intimately discuss their medical and personal experiences of life with this disease.

Executive Producer	Julie Raskin
Producers	Julie Raskin and Madeline Till
Director	Madeline Till
Director of Photography	Andreas Santamaria

## Order Form

Name			
Address			
City, State, Country			
Zip or Country Code			
Phone Number			
Email Address			
Please add me to your e-mail list	YES <input type="checkbox"/>	NO <input type="checkbox"/>	
<b>Item</b>	<b>Number of Copies</b>	<b>Cost Per Copy</b>	<b>Total</b>
1 Videotape for US (NTSC)		\$25 USD	\$
1 Videotape Int'l (PAL)		\$25 USD	\$
1 DVD for all formats		\$25 USD	\$
<b>Shipping</b>			
1 tape/DVD	US Domestic	\$10 USD	\$
	Canada	\$12 USD	\$
	International	\$20 USD	\$
Each additional tape/DVD	US/Canada	\$3 USD/tape or DVD	\$
	International	\$4 USD/tape or DVD	\$
		<b>TOTAL COST*</b>	<b>\$</b>

\*Please send U.S. dollar check or money order made payable to the *Center for Biopeacekeeping, 11 Summit Street, Glen Ridge, NJ, 07028*. If you are ordering from overseas, please send checks from a US bank or its affiliate in US dollars or request a foreign draft from your bank drawn on US dollars from a US bank.

Please expect delivery 1-4 weeks from date order is received.

If you have any questions, call Julie Raskin at (973) 566-0334 or e-mail at [jvraskin@aol.com](mailto:jvraskin@aol.com).

## **THE HI REFERENCE chart**

The HI chart is intended for all those who wish to know more about other children with HI. The chart gathers information about children with HI, everything from how much they weighed at birth to the medications they currently take. By gathering and sharing this information among HI families, we are able to learn from the experience of others. In particular, the chart is a great reference for those who participate in the hyperinsulinism yahoo group. As we communicate with each other online, we are able to keep track of the important characteristics of each child.

The chart is distributed only to those who contribute to it. In order to receive the chart you must first agree to offer information about your children with HI. By sending your information you are added on the chart and can then receive it. This is a way of showing respect to those that have already shared information.

The following is a questionnaire covering the information that is provided by the chart. If you want to be added to the chart you simply have to fill in the questionnaire and send it to the address below. You don't need to answer everything, just what you want to appear on it (but the more the better).

You will find that some questions are quite technical. This is in response to Dr. Aguillar who is trying to make use of our information to make advances in her genetic research on HI.

Once your family is included in the chart, you will receive a newly updated copy of it every time it is updated. The chart is distributed only to those that contribute to its data, and also to medical professionals that take an interest in it.

If you want more information about the chart or want to send in your information please contact :

Isabel Calderon  
By Email at [biovelo@cgocable.ca](mailto:biovelo@cgocable.ca)  
or use the link through our website at [www.surl.org](http://www.surl.org)

### Questionnaire for the PHHI reference chart

Parents' names	
Child's name	
Home (state or town, country)	
DOB (yyyy-mm-dd)	
Birth Weight	
Gestation length (weeks)	
Agpar	
Siblings	
Age first symptoms	
Age when diagnosed	
Pancreatectomy	
% pancreatectomy	
Age at first pancreatectomy	
Age at second pancreatectomy	
Age at 3rd pancreatectomy	
Histopathological results	
Portal veinous sampling?	
Calcium test?	
Brain damage or other related problems	
Medication (type, dose and mode of administration)	
Medications that failed	
Age treatment stopped (if that is the case)	
Tube feeding	
Feeding problems	
Genetic testing	
Special diet	
Contact (Email, address or phone number if you want people to be able to contact you directly)	
Drs name and hospital	
Did you have a glucose tolerance test during pregnancy? If so, what were the results at 1 hour, 2 hours, and 3 hours?	
Other remarks (type of PHHI and more)	