U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Gillis D. Familial Hyperinsulinism. 2003 Aug 19 [Updated 2019 Mar 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Familial Hyperinsulinism

Synonyms: Congenital Hyperinsulinism (CHI), Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI)

David Gillis, MD[1]

Created: August 19, 2003; Updated: March 21, 2019.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding familial hyperinsulinism (referred to as FHI in this *GeneReview*) and its genetic causes and management. The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of FHI.

Goal 2

Review the genetic causes of FHI.

Goal 3

Provide an evaluation strategy to identify the genetic cause of FHI in a proband (when possible).

Goal 4

Inform (when possible) medical management of FHI based on genetic cause and evaluation of relatives at risk.

Goal 5

Inform risk assessment and surveillance of at-risk relatives for early detection and treatment of FHI.

1. Clinical Characteristics of Familial Hyperinsulinism

Clinical Manifestations

Familial hyperinsulinism (FHI) is characterized by hypoglycemia that ranges from severe neonatal onset to childhood onset with mild symptoms. Neonatal-onset disease manifests within hours to days after birth. In the

Author Affiliation: 1 Hadassah Hebrew University Hospital, Jerusalem, Israel; Email: dgillis@hadassah.org.il.

newborn period, presenting symptoms may be nonspecific, including seizures, hypotonia, poor feeding, and apnea. Childhood-onset disease manifests during the first months or years of life and can present with an unprovoked seizure or laboratory evidence of hypoglycemia noted during acute illness during which nutritional intake is reduced. Some individuals may be asymptomatic. Even within the same family, disease manifestations can range from mild to severe and clinical presentation can range from immediately after birth to late in childhood.

Laboratory Features

In most individuals, FHI can be definitively and rapidly diagnosed if the appropriate laboratory tests are done on blood and urine samples during an episode of spontaneous hypoglycemia or during monitored fasting (glucose <50 mg/dL) (see Table 1).

Table 1. Diagnostic Tests for Documentation of Hyperinsulinism

Specimen Type	Laboratory Test	Expected Result in Hyperinsulinism
Blood	Insulin	Inappropriately elevated
	C-peptide	Elevated
	Free fatty acids	Inappropriately low
	β-hydroxybutyrate	Inappropriately low
	Acetoacetate	Inappropriately low
	Lactic acid	Normal
	Carnitine	Normal
	Growth hormone	Elevated due to hypoglycemia
	Cortisol	Elevated due to hypoglycemia, although not always, particularly if hypoglycemia is of short duration [1]
	T_4, T_3, TSH	Normal
	Ammonia	Elevated in hyperinsulinism/hyperammonemia syndrome only
Urine	Ketone bodies (at time of hypoglycemia)	Negative
	Reducing substances	Negative
	C-peptide	Elevated

TSH = thyroid-stimulating hormone
Reprinted from Glaser et al [1999] with permission from Elsevier
1. Hussain et al [2003]

Glucagon stimulation test. A glycemic response of >30 mg/dL following injection of 0.03 mg/kg glucagon excludes a primary hepatic or metabolic defect and is virtually pathognomonic for hyperinsulinism.

Calculate glucose requirement. A requirement of >15 mg/kg/min is highly suggestive of HI (normal requirements: neonate 5-8 mg/kg/min; older infant or child 3-5 mg/kg/min).

Note: Provocative tests with insulin secretagogues may be dangerous and are contraindicated.

Severe disease. In a newborn or young infant with severe disease that appears shortly after birth, the diagnosis of FHI can be based on documentation of inappropriately elevated plasma insulin concentration (>14.4 pmol/L [2 µU/mL]) in the presence of symptomatic hypoglycemia (plasma glucose concentration <2.7 mmol/L [50 mg/dL]).

Note: (1) "Inappropriately elevated insulin levels" are difficult to define, largely because of marked differences in specificity and sensitivity of commercial insulin assays. The concentrations mentioned here and in the literature must not be taken as hard cutoffs. (2) Pathologic hypoglycemia levels are not defined in any age group, particularly newborns.

Mild disease. In some individuals, particularly those with milder disease appearing after the first few days or weeks of life, fasting plasma insulin concentrations may fluctuate greatly, and the presence of pathologically elevated insulin concentrations may be difficult to demonstrate convincingly. In these individuals, the following surrogate measurements of insulin action can be useful:

- Inappropriate hypoketonemia (free fatty acid concentration <1.5 mmol/L)
- Exaggerated glycemic response to glucagon (>1.7 mmol/L [30 mg/dL] at a time of hypoglycemia)
- A markedly elevated glucose requirement to prevent hypoglycemia (i.e., exogenous glucose requirements that may exceed 15-20 mg/kg/min [normal: 5-8 mg/kg/min])

Imaging

Fluoro-DOPA positron emission tomography (F-DOPA-PET) has been used successfully for the preoperative localization of focal lesions [Otonkoski et al 2006, Mohnike et al 2008a].

Histology

Pancreatic beta cells (comprising <2% of all pancreatic cells) synthesize, store, and secrete insulin. Beta cells are located within the islets of Langerhans. Two major pancreatic histologic types ("diffuse" and "focal") have been described in individuals with FHI. A third histologic form ("atypical" or "mosaic") has also been described, although the genetic etiology of this form of FHI has not yet been discovered [Sempoux et al 2011]:

- **Diffuse** involvement of beta cells throughout the pancreas. Seen in approximately 60%-70% of individuals, diffuse disease is characterized by essentially normal neonatal pancreatic architecture. All beta cells are affected and many have large nuclei, abundant cytoplasm, and histologic evidence of increased metabolic activity.
- **Focal** pancreatic adenomatous hyperplasia. Seen in approximately 30%-40% of individuals, focal changes involve a limited region of the pancreas, with the remainder of the tissue being both histologically and functionally normal. A focal lesion is the confluence of apparently normal islets. Focal lesions typically are not macroscopically visible; they differ from true adenomas, which can be identified on gross inspection of the pancreas. Beta cells outside the focal lesion have small nuclei and sparse cytoplasm-histologic evidence that they are suppressed and not actively producing and secreting insulin.
- **Mosaic** involvement of the pancreatic islets. Pancreatic histology reveals the coexistence of two types of islets: large islets with cytoplasm-rich beta cells and occasional enlarged nuclei alongside shrunken islets with beta cells exhibiting little cytoplasm and small nuclei. Large islets are mostly confined to a few lobules, suggesting that removal of these particular lobules by partial pancreatectomy could result in a cure [Sempoux et al 2011]. The genetic etiology of this form of FHI is not known.
- Note: With the current availability of imaging and molecular genetic testing, diagnosis and management decisions do not require histology. Biopsy is not part of the initial evaluation, and the pancreatic histology is only known if surgical management is warranted.

Prognosis

If medical treatment can be safely maintained, glycemic control usually becomes easier with time, and most individuals treated medically enter clinical remission after several months or years of treatment [Mazor-Aronovitch et al 2009]. It is generally accepted that those individuals who respond well to medical treatment can be treated chronically without undue risk for long-term complications. Long-term follow up of medically treated

individuals shows that some eventually develop glucose intolerance, which can be effectively managed with mild dietary restrictions [Mazor-Aronovitch et al 2009].

2. Genetic Causes of Familial Hyperinsulinism

Familial hyperinsulinism (FHI) is the most common cause of persistent neonatal hypoglycemia and should be considered in every infant presenting with unexplained hypoglycemia. Pathogenic variants in 14 genes have been associated with FHI (Table 2). However, 40% of probands with FHI do not have an identified molecular cause.

Table 2. Familial Hyperinsulinism: Genes and Distinguishing Clinical Features

Gene [1, 2]	% of FHI Attributed to Pathogenic Variants in Gene	MOI	Distinguishing Clinical Features
ABCC8 [3]	40%-45% [4, 5]	AR	• Large for gestational age • Severe refractory hypoglycemia in the 1st 48 hrs of life • Respond only partially to diet or diazoxide & may require pancreatic resection • 40% have focal form. • Diabetes may develop later in life. • Founder variants in Ashkenazi Jewish & Finnish populations [6]
		AD	• Appropriate for gestational age at birth • Present at age ~1 yr (range: 2 days – 30 yrs) • Respond to diet & diazoxide therapy, exceptions reported • Variable penetrance
CACNA1D	1 person [7]		• Persistent diazoxide-responsive hypoglycemia • Mild aortic insufficiency • Severe hypotonia & developmental delay
GCK	<1% [8]	AD	• Ranges from mild diazoxide-responsive hypoglycemia to severe, diazoxide-unresponsive hypoglycemia. • Insulin secretion in response to elevation & suppression of glucose levels is qualitatively normal, but the glucose set-point at which insulin secretion is turned off is abnormally low.
GLUD1	5% [9]	AD	Hyperammonemia/hyperinsulinism syndrome: • Mild-to-moderate hyperammonemia (1.5-4.0x upper limit of normal) • Ammonia levels are not related to ambient glucose levels or to duration of fasting & appear to be benign. • Mild hypoglycemia usually presents after neonatal period. • May be assoc w/exquisite sensitivity to leucine challenge • Most respond well to diazoxide; only a minority require surgery to prevent recurrent hypoglycemia.

Table 2. continued from previous page.

Gene [1, 2]	% of FHI Attributed to Pathogenic Variants in Gene	MOI	Distinguishing Clinical Features
HADH	<1% [10, 11]	AR	• ↑ urine 3-hydroxyglutaric acid & serum 3-hydroxybutyryl-carnitine • Severe hypoglycemia after leucine administration • Mild diazoxide-responsive hypoglycemia; severe hypoglycemia has been reported. • Normal urinary 3-hydoxyglutaric acid & normal plasma acylcarnitine profile does not exclude the diagnosis.
HK1	1 family [12]	AD	• Diagnosed w/FHI before age 1 yr • 40% presented w/seizure • Diazoxide responsive • Failed to adequately suppress insulin secretion following oral glucose tolerance test or prolonged fasting • Not leucine sensitive
HNF1A	Unknown	AD	• Large for gestational age • Mild diazoxide-sensitive hypoglycemia • Hypoglycemia usually resolves in childhood. • MODY3 develops in adolescence or adulthood.
HNF4A	5% [13]	AD	• Large for gestational age • Mild diazoxide-sensitive hypoglycemia • Hypoglycemia sometimes transient • Insulinopenic diabetes mellitus during adolescence
KCNJ11 [3]	5% [15]	AR	• Large for gestational age • Severe refractory hypoglycemia in 1st 48 hrs of life • Affected infants usually respond only partially to diet or diazoxide therapy; may require pancreatic resection. • 40% have focal form.
		AD	• Appropriate for gestational age at birth • Present at age ~1 yr (range: 2 days – 30 yrs) • Respond to diet & diazoxide therapy; exceptions reported • Variable penetrance
PMM2	11 families [14]		• Assoc w/polycystic kidney disease in all persons • ~50% also have hepatic cysts. • Diazoxide responsive • Assoc w/late-infantile seizures w/o neurologic damage
SLC16A1	Unknown	AD	• Hypoglycemia occurs during childhood or later. • Severe hypoglycemia occurring after anaerobic & not aerobic exercise
UCP2	2% of diazoxide-responsive HI [16]	AD	• Mild diazoxide-responsive hypoglycemia • Children reported w/hypoglycemia 4 hrs after glucose intake • Recently questioned as a monogenic cause of hypoglycemia [17]

Table 2. continued from previous page.

Gene [1, 2]	% of FHI Attributed to Pathogenic Variants in Gene	MOI	Distinguishing Clinical Features
Unknown	40%	NA	

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. *ABCC8*- and *KCNJ11*-related FHI are also known as FHI-K_{ATP}.
4. Nestorowicz et al [1998], Aguilar-Bryan & Bryan [1999], Meissner et al [1999], Fournet & Junien [2003], Tornovsky et al [2004]
5. A few exon or multiexon deletions have been reported in *ABCC8* (see Table A).
6. In the Ashkenazi Jewish population, two *ABCC8* founder variants, p.Phe1387del and c.3989-9G>A, are responsible for approximately 97% of FHI [Glaser et al 2011]. *ABCC8* founder variants present in the Finnish population include p.Val187Asp and p.Glu1506Lys [Otonkoski et al 1999, Huopio et al 2000].
7. Flanagan et al [2017]
8. Glaser et al [1998], Christesen et al [2002], Cuesta-Muñoz et al [2004], Sayed et al [2009]
9. Stanley et al [2000], Bahi-Buisson et al [2008]
10. Clayton et al [2001], Molven et al [2004], Di Candia et al [2009]
11. Rare large deletions including exon 1 have been reported [Flanagan et al 2011].
12. Pinney et al [2013]
13. Flanagan et al [2010]
14. Cabezas et al [2017]
15. Thomas et al [1996], Nestorowicz et al [1997], Tornovsky et al [2004]
16. Ferrara et al [2017] have recently shown variable phenotype by age with children developing post-glucose-challenge hypoglycemia.
17. Laver et al [2017] claim, based on studies including large numbers of variants in this gene, that the variants may act as low-effect risk factors, and that in vitro evidence of a role in insulin secretion for this protein is not proof of monogenic disease.

Other Disorders to Consider in the Differential Diagnosis of Familial Hyperinsulinism

Hyperinsulinemic hypoglycemia can be seen in disorders other than FHI. Furthermore, neonatal hypoglycemia can be caused by non-insulin-mediated mechanisms, in which case plasma insulin concentrations are low and plasma glucose concentrations can be readily corrected with normal replacement doses of glucose (5-8 mg/kg/min).

Table 3. Other Disorders to Consider in the Differential Diagnosis of Familial Hyperinsulinism (FHI)

Disorder	Gene(s) or Locus	MOI	Clinical Features of the Disorder Distinguishing from FHI
Hyperinsulinemic hypoglycemia			
Infants of diabetic mother	NA	NA	Hypoglycemia is transient, resolving w/in days to wks after birth.
Transient hyperinsulinemic hypoglycemia of infancy	Unknown	NA	• Typically responds well to diazoxide therapy • May occur after history of perinatal stress or asphyxia
Beckwith-Wiedemann syndrome	*CDKN1C* 11p15	AD or sporadic	Typically mild & responds to medical treatment w/ diazoxide
Familial hyperinsulinemic hypoglycemia type 5 (OMIM 609968)	*INSR*	AD	Postprandial hypoglycemia occurs 3-5 hrs after meals.
INSR-related severe syndromic insulin resistance [1]	*INSR*	AR	Fasting hypoglycemia assoc w/insulin resistance syndrome
Insulinoma (sporadic or due to multiple endocrine neoplasia type 1)	*MEN1*	AD or sporadic	Onset typically age >1 yr

Table 3. continued from previous page.

Disorder	Gene(s) or Locus	MOI	Clinical Features of the Disorder Distinguishing from FHI
Hypoglycemia w/o hypersinulinemia			
21-hydroxylase-deficient congenital adrenal hyperplasia	*CYP21A2*	AR	• Typically ketotic hypoglycemia, suppressed plasma insulin levels, & blunted glycemic response to glucagon. Hypoglycemia typically mild • Congenital deficiency of cortisol • Responds to steroid therapy
NR0B1-related adrenal hypoplasia congenita	*NR0B1*	XL	• Primary adrenal insufficiency • Hypogonadotropic hypogonadism
Pituitary hormone deficiencies (OMIM PS613038)	Many	AR AD	• Hypoglycemia typically mild • Responds to growth hormone
Glycogen storage diseases (See Glycogen Storage Disease Type I.)	Many	AR XL	Fasting hypoglycemia
Gluconeogenesis disorders (See fructose 1,6-biphosphatase deficiency, OMIM 229700)	Many	AR	Hypoglycemia primarily during fasting or intercurrent illness w/lactic acidosis
Hyperammonemia/hyperinsulinism			
Disorders of fatty acid oxidation (See MCAD Deficiency.)	Many	AR AD XL	• Fasting hypoketotic hypoglycemia • Myopathy &/or cardiomyopathy • Acute symptoms precipitated by fasting or acute illness • Acylcarnitine profile on tandem mass spectrometry may be diagnostic.
Urea cycle disorders	Many	AR XL	• Hyperammonemia • Absence of hyperinsulinism

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NA = not applicable; XL = X-linked
1. Ben Abdelaziz et al [2016]

3. Evaluation Strategies to Identify the Genetic Cause of Familial Hyperinsulinism in a Proband

Establishing a specific genetic cause of familial hyperinsulinism (FHI):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history. There are few points in the history that can help differentiate specific genetic causes of FHI. However, ethnic background can increase the probability of some forms (e.g., *ABCC8* founder variant in Ashkenazi Jewish individuals). Hypoglycemia occurring postprandially, particularly after protein-rich meals, with relatively stable overnight glycemia may suggest a *GLUD1* pathogenic variant. A robust response to a low dose of diazoxide is unusual in individuals with biallelic *ABCC8* or *KCNJ11* pathogenic variants but typical of most other types of FHI. See Table 2 for additional findings that may suggest specific types of FHI. A history of severe hypoglycemia occurring after anaerobic exercise is suggestive of FHI type 7 (see Table 3).

Physical examination. There are no phenotypic findings on physical examination that can differentiate the different genetic causes of FHI.

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of FHI and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel or single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

A multigene panel that includes some or all of the genes listed in Table 2 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Serial single-gene testing can be considered if clinical findings and/or family history indicate that pathogenic variants in a particular gene are most likely (see Table 2).

- Individuals of Ashkenazi Jewish descent: *ABCC8* pathogenic founder variants
  - p.Phe1387del
  - c.3989-9G>A
- Individuals of Finnish descent: *ABCC8* pathogenic founder variants
  - p.Val187Asp
  - p.Glu1506Lys
- Individuals with elevated serum ammonia: *GLUD1* pathogenic variants. Note: Sequencing of exons 6, 7, 10, 11, and 12 identifies virtually all pathogenic variants in this gene, although it is possible that causative variants occur in other exons as well.

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Medical Management of FHI Based on Genetic Cause

Initial Treatment

Once initial diagnostic blood samples are obtained, the hypoglycemia must be corrected immediately using intravenous glucose at a dose sufficient to prevent further hypoglycemia and irreversible brain damage. The dose of glucose may be high (>15 mg/kg/min) and frequently requires central venous access. The definition of adequate glucose control has been the subject of discussion. Most investigators recommend maintaining all glucose levels >3.3 mmol/L (60 mg/dL), a level that leaves a sufficient margin to prevent frequent episodes of

neuroglycopenia (i.e., transient or permanent brain dysfunction caused by inadequate glucose supplies) [Burns et al 2008, Inder 2008].

Long-Term Medical Management

The next phase of treatment, designed to decrease and eliminate parenteral glucose requirement, is empiric and involves a combination of medical therapies. Some individuals, particularly those with *GLUD1*-, *HADH*-, or *GCK*-related FHI or dominant pathogenic variants in either *ABCC8* or *KCNJ11*, respond very well to medical therapy. Individuals with severe FHI-K_{ATP} (autosomal recessive pathogenic variants in *ABCC8* or *KCNJ11*) may also respond to medical therapy; however, these individuals often require aggressive medical management, including a combination of several of the drugs mentioned below along with dietary intervention (that may even require the use of frequent gastrostomy feeds for several years) to maintain plasma glucose concentration in a clinically safe range without the use of parenteral glucose administration. This management protocol may be extremely demanding and, even if successful in the hospital setting, may not be appropriate for many families on an outpatient basis. The overall success of medical management in FHI-K_{ATP} is extremely variable [Mazor-Aronovitch et al 2009].

- **Diazoxide,** which binds to the ABCC8 subunit of the K_{ATP} channel, increases the channel's probability of being open, resulting in membrane hyperpolarization and inhibition of insulin release. Some evidence suggests that diazoxide binding to mutated channels may correct abnormal protein folding and thus facilitate the transit of more channels to the membrane. The effective therapeutic dose varies but may be as high as 20 mg/kg/day in divided doses. A thiazide diuretic should be given along with diazoxide with doses >8-10 mg/kg/day to prevent fluid retention, which may be severe [Hussain et al 2004].
- **Somatostatin analogs** (e.g., octreotide or lanreotide) suppress insulin secretion by binding to specific beta-cell receptors and initiating a number of intracellular signaling pathways. The clinical efficacy of octreotide may be limited by the relatively short duration of inhibition of insulin secretion after subcutaneous bolus injection (~3 hours) and by the fact that these drugs also inhibit glucagon and growth hormone secretion, thus impairing hepatic glucose production. Careful attention to dosage (typically 10-15 µg/kg/day for octreotide) as well as the use of continuous subcutaneous injection using a portable pump greatly enhances clinical efficacy [Hussain et al 2004]. Simultaneous treatment with glucagon may enhance efficacy. Long-acting analogs including LAR octreotide [Le Quan Sang et al 2012] and lanreotide [Modan-Moses et al 2011] can be used after the hypoglycemia becomes manageable and stable, usually after age three to four years.
- **Nifedipine,** which acts as an inhibitor of the voltage-dependent calcium channels present in the beta cell, inhibits insulin secretion by decreasing calcium influx [Hussain et al 2004]. In vitro, this drug effectively suppresses insulin secretion depending on the pathogenic variant; however, in vivo side effects are usually dose limiting, and the drug is only rarely clinically effective.
- **Glucagon,** which increases hepatic gluconeogenesis, helps prevent hypoglycemia. The drug can be used acutely to treat severe hypoglycemia, or chronically as replacement therapy to counteract suppression by somatostatin analogs, but this therapy is hampered by crystallization of the glucagon in continuous subcutaneous infusion sets [Mohnike et al 2008b].
- **Recombinant IGF-I** has been shown to suppress insulin secretion in individuals with FHI [Katz et al 1999]; however, therapeutic success has not been confirmed.
- **Glucocorticoids** induce resistance to endogenous insulin and correct the inadequate cortisol response sometimes seen in affected individuals. Their use in the treatment algorithm of FHI is, however, very limited.
- **Growth hormone** may be given in combination with somatostatin analogs in order to counteract growth hormone suppression by the analogs. However, this is rarely needed as the dose of somatostatin analogs is usually reduced during childhood as the condition improves, so that growth suppression is not a significant clinical issue.

- **Dietary intervention**
  - Frequent high-carbohydrate feedings, including formula supplemented with glucose polymer
  - Nighttime continuous gastric drip containing glucose or glucose polymer
  - Feeding gastrostomy to simplify the process of continuous nighttime feeding and to provide access for emergency home treatment of hypoglycemia

Surgical Management

Once an individual is stabilized, a decision must be made as to the need for surgical intervention and the extent of such intervention. In some severe cases, even the most aggressive medical management fails to maintain plasma glucose concentration consistently within the safe limits (>60 mg/dL). In such individuals, surgery must be considered. Prior to surgical intervention, differentiation between focal and diffuse disease using one of the following techniques is important, as the surgical approach and the clinical outcome are quite different:

- **Genetic studies,** in certain circumstances, can be useful in differentiating focal from diffuse disease:
  - Finding two recessive pathogenic variants or a single dominant pathogenic variant is diagnostic of diffuse disease.
  - Finding a single recessive pathogenic variant on the maternal allele suggests diffuse disease; it is assumed that the other pathogenic variant on the paternal allele was missed because of technical limitations of the molecular genetic testing.
  - Finding a single recessive pathogenic variant on the paternal allele is consistent with and highly suggestive of focal disease, although it cannot be considered diagnostic, as molecular genetic testing methods could have failed to detect a pathogenic variant on the maternal allele. In such individuals, further testing to diagnose and localize focal disease is indicated.

    Because of the large size of *ABCC8* and *KNCJ11*, complete sequencing and analysis of all variants discovered is expensive and time-consuming and may not be completed in time to aid in clinical decision making for a severely ill individual. With the incorporation of modern sequencing techniques, rapid complete sequencing of all relevant genes is becoming feasible. In contrast, for a person from an ethnic group with a known founder variant (e.g., Ashkenazi Jews), targeted analysis for pathogenic variants can provide rapid and inexpensive clinically useful information.
- **Fluoro-DOPA positron emission tomography (F-DOPA-PET)** has been used successfully for the preoperative localization of focal lesions [Otonkoski et al 2006, Mohnike et al 2008a] (see Clinical Manifestations). While the scan itself is relatively easy to perform, the radiopharmaceutical is not readily available in many centers and the scan can be difficult to interpret, requiring extensive experience to obtain reliable results.
- **Intraoperative histologic evaluation of a pancreatic biopsy** in very experienced hands can be used to differentiate between diffuse FHI and a normal, suppressed pancreas in an individual with a focal lesion. Since intraoperative identification of the focal lesion can be very difficult or impossible, resection of the lesion is usually only possible if its location is determined preoperatively.

Individuals with diffuse disease require extensive (80%-95%) pancreatic resection and are at risk for persistent hypoglycemia postoperatively and/or insulin-requiring diabetes mellitus later in childhood. Individuals with focal disease can be cured by localized resection of the hyperplastic region. Although the apparent risk for postoperative diabetes appears to be very low after limited pancreatectomy, very long-term follow up is not yet available on these individuals [Beltrand et al 2012]. Since focal lesions can only rarely be identified grossly at the time of surgery, perioperative diagnosis and localization of focal lesions is needed.

Surveillance

In persons with clinically mild disease, episodes of subtle, undiagnosed hypoglycemia can cause permanent brain damage. Therefore, close monitoring and vigilance is just as critical in mild cases as it is in severe cases. Furthermore, in persons with mild disease and in those with severe disease in clinical remission, severe hypoglycemia may be precipitated by intercurrent viral illness. Thus, it is imperative that parents monitor glucose concentrations closely especially during intercurrent illness, even in the absence of symptomatic hypoglycemia. Identification of the genetic cause of FHI can help guide the frequency of blood glucose testing. Individuals who are diazoxide responsive and take their medication regularly will need less frequent glucose monitoring than non-diazoxide-responsive individuals. In the first few years of life, use of continuous glucose monitoring is recommended for children with very unstable glucose levels regardless of the genetic cause.

Agents/Circumstances to Avoid

Prolonged fasting of any sort should be avoided. Emergency treatment options for hypoglycemia must be available at all times in case of an unexpected hypoglycemic episode.

Pregnancy Management

Affected individuals who previously underwent near-total or sub-total pancreatectomy typically have insulin-requiring diabetes by the time they become pregnant. In this case, treatment is the same as for individuals with preexisting diabetes from any cause. There is little, if any, experience with pregnancy in individuals who were treated conservatively or who underwent limited pancreatectomy for focal FHI, as these treatments are relatively new. In this situation, close monitoring of glucose to detect both recurrent hypoglycemia and hyperglycemia is warranted. If hyperglycemia is documented, treatment should be instituted as for any woman with gestational diabetes. A fetus at risk for FHI should be monitored for size and weight. Excessive fetal weight gain during the last trimester of pregnancy increases the risk of obstetric complications and of cesarean delivery. In pregnant women with a history of FHI and gestational hyperglycemia due to prior surgical treatment, the fetus should be monitored as for any case of preexisting type 1, preexisting type 2, or gestational diabetes.

See MotherToBaby for further information on medication use during pregnancy.

5. Risk Assessment and Surveillance of At-Risk Relatives for Early Detection and Treatment of FHI

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Genetic Risk Assessment

Familial hyperinsulinism (FHI) can be inherited in an autosomal recessive or autosomal dominant manner.

- FHI-K_{ATP}, caused by pathogenic variants in either *ABCC8* or *KCNJ11*, is most commonly inherited in an autosomal recessive manner, and rarely in an autosomal dominant manner.
- FHI-CACNA1D, FHI-GCK, FHI-GLUD1, FHI-HK1, FHI-HNF1A, FHI-HNF4A, and FHI-UCP2 are inherited in an autosomal dominant manner.
- FHI-HADH and FHI-PMM2 are inherited in an autosomal recessive manner.

- The focal form of FHI is caused by pathogenic variants in *ABCC8* or *KCNJ11* and is inherited in what can be defined, officially, as an autosomal dominant manner; however, the focal form of FHI is associated with markedly reduced penetrance and is a biologically low-risk occurrence among individuals who are heterozygous for a paternal pathogenic variant.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one pathogenic variant).
- Heterozygotes (carriers) are typically asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
- Sibs heterozygous for a paternally derived *ABCC8* or *KCNJ11* pathogenic variant are at a 1:540 risk for focal FHI (see AD Focal Form – Risk to Family Members, **Sibs of a proband**) [Glaser et al 2011]. This risk is expected to be independent of the specific pathogenic variant involved [Glaser et al 2011].

Offspring of a proband

- The offspring of an individual with autosomal recessive FHI are obligate heterozygotes (carriers) for a pathogenic variant.

  Heterozygous offspring of a male proband are at risk of developing focal FHI (see AD Focal Form – Risk to Family Members, **Offspring of a proband**).

- The risk to offspring of being affected with autosomal recessive FHI depends on the carrier frequency in the reproductive partner's ethnic group. In most cases, the carrier frequency appears to be approximately 1% or less; however, genetic isolates with very high carrier frequency have been reported. In Ashkenazi Jews, for example, the carrier rate is estimated at 1:52; the risk to the child of a proband and an individual of Ashkenazi Jewish descent would be approximately 1:104, or 1% [Glaser et al 2011].

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Autosomal Dominant Inheritance, Diffuse Form – Risk to Family Members

Parents of a proband

- One of the parents of an affected child may be heterozygous for a pathogenic variant, and thus be affected by FHI.
- More typically, a proband with HI has the disorder as the result of a *de novo* gene pathogenic variant.
  - The proportion of cases caused by *de novo* pathogenic variants is estimated at approximately 75% for HA/HI.
  - Neither of the two families with FHI-GCK reported by Glaser et al [1998] or Christesen et al [2002] were *de novo* in the proband's generation. However, Cuesta-Muñoz et al [2004] and Martinez et al [2017] each reported *de novo* activating *GCK* pathogenic variants that resulted in severe hyperinsulinemia in female infants.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing, and, if positive, clinical testing for fasting and postprandial hypoglycemia.

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with autosomal dominant FHI may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for FHI because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with FHI has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has the pathogenic variant, the parent's family members are at risk.

Autosomal Dominant Inheritance, Focal Form – Risk to Family Members

Parents of a proband

- The fathers of individuals with focal FHI are heterozygous for an *ABCC8* or *KCNJ11* pathogenic variant. Given the low risk for a person with such a variant of having focal disease (estimated at 1:540 due to a somatic loss of maternal allele in a single cell [Glaser et al 2011]), the chance that both father and child will be affected is less than 1:250,000. Thus, for practical purposes the fathers do not have focal FHI. The pathogenic variants responsible for autosomal dominant diffuse FHI are not associated with focal HI.
- Although no instances of focal FHI caused by a *de novo* pathogenic variant on the paternally derived *ABCC8* or *KCNJ11* allele have been reported, it remains a possibility.

Sibs of a proband

- Sibs of a proband with focal FHI have a 50% chance of inheriting the pathogenic variant from their father. However, the focal form of FHI manifests only when the pathogenic variant occurs on the paternally derived allele and a separate, independent somatic event results in the loss of the maternal allele (loss of heterozygosity).
- The risk for focal FHI in a sib of a proband has been estimated at 1:540 [Glaser et al 2011].

Offspring of a proband

- Each child of an individual with focal FHI has a 50% chance of inheriting the pathogenic variant.

- The risk to offspring of having the diffuse form of hyperinsulinemia is related to the carrier frequency in the reproductive partner's ethnic group, as offspring will have this form of hyperinsulinemia only if they inherit a pathogenic variant from both parents.
- Each child of a male proband with focal FHI is also at risk of developing focal FHI. To develop FHI, the individual must inherit the pathogenic variant from the father (50% chance) and a second somatic event must occur, the latter being quite uncommon. The estimated risk for focal FHI to the offspring of a male proband with focal FHI is 1:540 [Glaser et al 2011].

Other family members. The sibs of the father of a proband with focal FHI may also carry an *ABCC8* or *KCNJ11* pathogenic variant. However, the focal form of FHI manifests only when the pathogenic variant occurs on the paternally derived allele and a somatic event resulting in the loss of the maternal allele occurs (loss of heterozygosity).

Evaluation of Relatives at Risk

It is appropriate to clarify the clinical/genetic status of sibs of an affected individual so that appropriate evaluation and treatment can be initiated before hypoglycemia occurs. Because of the severe neurologic consequences of delayed diagnosis and treatment, it is imperative that at-risk newborns be followed closely from birth and a definitive diagnosis made as rapidly as possible. Evaluations can include the following:

- Molecular genetic testing if the pathogenic variant(s) in the family are known. (Note: If the causative pathogenic variants have been identified in a proband, it is prudent to test all at-risk relatives; depending on the findings, more extensive family investigations may be warranted.)
- If the pathogenic variant in the family is not known, careful glucose monitoring of newborns thought to be at risk based on the inheritance pattern should be undertaken and parents should be aware of signs of hypoglycemia that would require investigation during childhood.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Related Genetic Counseling Issues

Mode of inheritance when no pathogenic variant is identified. Approximately 40% of individuals with HI do not have an identifiable pathogenic variant in any of the genes known to be associated with HI. Risk to family members in these families is not known.

Family planning – autosomal recessive inheritance

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Because of the relatively high prevalence of two specific *ABCC8* pathogenic variants in the Ashkenazi Jewish population, preconception genetic screening may be considered in this specific ethnic group. Similarly, such genetic screening may be considered in any ethnic group with a high carrier rate of known pathogenic variants.

Family planning – autosomal dominant inheritance

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing and preimplantation genetic testing for a pregnancy at increased risk for the diffuse form of FHI-K_{ATP} (involvement of beta cells throughout the pancreas) or for a pregnancy at increased risk of inheriting pathogenic variants causative of other types of diffuse FHI are possible. Parents who elect to continue a pregnancy in which the fetus has been determined to be affected have the advantage of initiating treatment immediately following birth, thus preventing early, severe hypoglycemia.

In families of individuals with focal FHI (pancreatic adenomatous hyperplasia that involves a limited region of the pancreas), prenatal testing is not informative: while the paternal pathogenic variant can be identified in the DNA of an at-risk fetus, no testing can identify which fetuses will also have a somatic event leading to loss of the maternal allele.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Congenital Hyperinsulinism International (CHI)**
  Phone: 973-544-8372
  Email: jraskin@congenitalhi.org
  www.congenitalhi.org
- **National Library of Medicine Genetics Home Reference**
  Congenital hyperinsulinism

Chapter Notes

Author History

David Gillis, MD (2019-present)

Benjamin Glaser, MD; Hadassah-Hebrew University Medical Center (2003-2019)

Revision History

- 21 March 2019 (sw) Comprehensive update posted live
- 24 January 2013 (me) Comprehensive update posted live
- 15 June 2010 (cd) Revision: prenatal testing for *HADH* mutations available on a clinical basis
- 23 February 2010 (me) Comprehensive update posted live
- 19 August 2003 (me) Review posted live
- 12 May 2003 (bg) Original submission

References

Literature Cited

Aguilar-Bryan L, Bryan J. Molecular biology of adenosine triphosphate-sensitive potassium channels. Endocr Rev. 1999;20:101-35. PubMed PMID: 10204114.

Bahi-Buisson N, Roze E, Dionisi C, Escande F, Valayannopoulos V, Feillet F, Heinrichs C, Chadefaux-Vekemans B, Dan B, de Lonlay P. Neurological aspects of hyperinsulinism-hyperammonaemia syndrome. Dev Med Child Neurol. 2008;50:945-9. PubMed PMID: 19046187.

Beltrand J, Caquard M, Arnoux JB, Laborde K, Velho G, Verkarre V, Rahier J, Brunelle F, Nihoul-Fékété C, Saudubray JM, Robert JJ, de Lonlay P. Glucose metabolism in 105 children and adolescents after pancreatectomy for congenital hyperinsulinism. Diabetes Care. 2012;35:198-203. PubMed PMID: 22190679.

Ben Abdelaziz R, Ben Chehida A, Azzouz H, Boudabbous H, Lascols O, Ben Turkia H, Tebib N. A novel homozygous missense mutation in the insulin receptor gene results in an atypical presentation of Rabson-Mendenhall syndrome. Eur J Med Genet. 2016;59:16–9. PubMed PMID: 26691667.

Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008;122:65-74. PubMed PMID: 18595988.

Cabezas OR, Flanagan SE, Stanescu H, García-Martínez E, Caswell R, Lango-Allen H, Antón-Gamero M, Argente J, Bussell AM, Brandli A, Cheshire C, Crowne E, Dumitriu S, Drynda R, Hamilton-Shield JP, Hayes W, Hofherr A, Iancu D, Issler N, Jefferies C, Jones P, Johnson M, Kesselheim A, Klootwijk E, Koettgen M, Lewis W, Martos JM, Mozere M, Norman J, Patel V, Parrish A, Pérez-Cerdá C, Pozo J, Rahman SA, Sebire N, Tekman M, Turnpenny PD, Hoff WV, Viering DHHM, Weedon MN, Wilson P, Guay-Woodford L, Kleta R, Hussain K, Ellard S, Bockenhauer D. Polycystic kidney disease with hyperinsulinemic hypoglycemia caused by a promoter mutation in phosphomannomutase 2. J Am Soc Nephrol. 2017;28:2529-39 PubMed PMID: 28373276.

Christesen HB, Jacobsen BB, Odili S, Buettger C, Cuesta-Munoz A, Hansen T, Brusgaard K, Massa O, Magnuson MA, Shiota C, Matschinsky FM, Barbetti F. The second activating glucokinase mutation (A456V): implications for glucose homeostasis and diabetes therapy. Diabetes. 2002;51:1240-6. PubMed PMID: 11916951.

Clayton PT, Eaton S, Aynsley-Green A, Edginton M, Hussain K, Krywawych S, Datta V, Malingre HE, Berger R, van den Berg IE. Hyperinsulinism in short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency reveals the importance of beta-oxidation in insulin secretion. J Clin Invest. 2001;108:457-65. PubMed PMID: 11489939.

Cuesta-Muñoz AL, Huopio H, Otonkoski T, Gomez-Zumaquero JM, Näntö-Salonen K, Rahier J, López-Enriquez S, García-Gimeno MA, Sanz P, Soriguer FC, Laakso M. Severe persistent hyperinsulinemic hypoglycemia due to a de novo glucokinase mutation. Diabetes. 2004;53:2164-8. PubMed PMID: 15277402.

Di Candia S, Gessi A, Pepe G, Sogno Valin P, Mangano E, Chiumello G, Gianolli L, Proverbio MC, Mora S. Identification of a diffuse form of hyperinsulinemic hypoglycemia by 18-fluoro-L-3,4 dihydroxyphenylalanine positron emission tomography/CT in a patient carrying a novel mutation of the HADH gene. Eur J Endocrinol. 2009;160:1019-23. PubMed PMID: 19318379.

Flanagan SE, Kapoor RR, Mali G, Cody D, Murphy N, Schwahn B, Siahanidou T, Banerjee I, Akcay T, Rubio-Cabezas O, Shield JP, Hussain K, Ellard S. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. Eur J Endocrinol. 2010;162:987-92. PubMed PMID: 20164212.

Flanagan SE, Patch AM, Locke JM, Akcay T, Simsek E, Alaei M, Yekta Z, Desai M, Kapoor RR, Hussain K, Ellard S. Genome-wide homozygosity analysis reveals HADH mutations as a common cause of diazoxide-responsive hyperinsulinemic-hypoglycemia in consanguineous pedigrees. J Clin Endocrinol Metab. 2011;96:E498-502. PubMed PMID: 21252247.

Flanagan SE, Vairo F, Johnson MB, Caswell R, Laver TW, Lango Allen H, Hussain K, Ellard S. A CACNA1D mutation in a patient with persistent hyperinsulinaemic hypoglycaemia, heart defects, and severe hypotonia. Pediatr Diabetes. 2017;18:320-3. PubMed PMID: 28318089.

Ferrara CT, Boodhansingh KE, Paradies E, Fiermonte G, Steinkrauss LJ, Topor LS, Quintos JB, Ganguly A, De Leon DD, Palmieri F, Stanley CA. Novel hypoglycemia phenotype in congenital hyperinsulinism due to dominant mutations of uncoupling protein 2. J Clin Endocrinol Metab. 2017;102:942-9. PubMed PMID: 27967291.

Fournet JC, Junien C. The genetics of neonatal hyperinsulinism. Horm Res. 2003;59 Suppl 1 :30-4.

Glaser B, Blech I, Krakinovsky Y, Ekstein J, Gillis D, Mazor-Aronovitch K, Landau H, Abeliovich D. ABCC8 mutation allele frequency in the Ashkenazi Jewish population and risk of focal hyperinsulinemic hypoglycemia. Genet Med. 2011;13:891-4. PubMed PMID: 21716120.

Glaser B, Kesavan P, Heyman M, Davis E, Cuesta A, Buchs A, Stanley CA, Thornton PS, Permutt MA, Matschinsky FM, Herold KC. Familial hyperinsulinism caused by an activating glucokinase mutation. N Engl J Med. 1998;338:226-30. PubMed PMID: 9435328.

Glaser B, Landau H, Permutt MA. Neonatal hyperinsulinism. Trends Endocrinol Metab. 1999;10:55-61. PubMed PMID: 10322395.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Huopio H, Reimann F, Ashfield R, Komulainen J, Lenko HL, Rahier J, Vauhkonen I, Kere J, Laakso M, Ashcroft F, Otonkoski T. Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. J Clin Invest. 2000;106:897-906. PubMed PMID: 11018078.

Hussain K, Aynsley-Green A, Stanley CA. Medications used in the treatment of hypoglycemia due to congenital hyperinsulinism of infancy (HI). Pediatr Endocrinol Rev. 2004;2 Suppl 1 :163-7. PubMed PMID: 16456495.

Hussain K, Hindmarsh P, Aynsley-Green A. Neonates with symptomatic hyperinsulinemic hypoglycemia generate inappropriately low serum cortisol counterregulatory hormonal responses. J Clin Endocrinol Metab 2003;88: 4342e7

Inder T. How low can I go? The impact of hypoglycemia on the immature brain. Pediatrics. 2008;122:440-1. PubMed PMID: 18676561.

Katz LE, Ferry RJ Jr, Stanley CA, Collett-Solberg PF, Baker L, Cohen P. Suppression of insulin oversecretion by subcutaneous recombinant human insulin-like growth factor I in children with congenital hyperinsulinism due to defective beta-cell sulfonylurea receptor. J Clin Endocrinol Metab. 1999;84:3117-24. PubMed PMID: 10487673.

Laver TW, Weedon MN, Caswell R, Hussain K, Ellard S, Flanagan SE. Analysis of large-scale sequencing cohorts does not support the role of variants in UCP2 as a cause of hyperinsulinaemic hypoglycaemia. Hum Mutat. 2017;38:1442-4. PubMed PMID: 28681398.

Le Quan Sang KH, Arnoux JB, Mamoune A, Saint-Martin C, Bellanné-Chantelot C, Valayannopoulos V, Brassier A, Kayirangwa H, Barbier V, Broissand C, Fabreguettes JR, Charron B, Thalabard JC, de Lonlay P. Successful treatment of congenital hyperinsulinism with long-acting release octreotide. Eur J Endocrinol. 2012;166:333-9. PubMed PMID: 22048969.

Mazor-Aronovitch K, Landau H, Gillis D. Surgical versus non-surgical treatment of congenital hyperinsulinism. Pediatr Endocrinol Rev. 2009;6:424-30. PubMed PMID: 19396028.

Meissner T, Beinbrech B, Mayatepek E. Congenital hyperinsulinism: molecular basis of a heterogeneous disease. Hum Mutat. 1999;13:351-61. PubMed PMID: 10338089.

Modan-Moses D, Koren I, Mazor-Aronovitch K, Pinhas-Hamiel O, Landau H. Treatment of congenital hyperinsulinism with lanreotide acetate (SomatulineAutogel). J Clin Endocrinol Metab. 2011;96:2312-7 PubMed PMID: 21697252.

Mohnike K, Blankenstein O, Minn H, Mohnike W, Fuchtner F, Otonkoski T. [18F]-DOPA positron emission tomography for preoperative localization in congenital hyperinsulinism. Horm Res. 2008a;70:65-72. PubMed PMID: 18547951.

Mohnike K, Blankenstein O, Pfuetzner A, Pötzsch S, Schober E, Steiner S, Hardy OT, Grimberg A, van Waarde WM. Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. Horm Res. 2008b;70:59-64. PubMed PMID: 18493152.

Molven A, Matre GE, Duran M, Wanders RJ, Rishaug U, Njølstad PR, Jellum E, Søvik O. Familial hyperinsulinemic hypoglycemia caused by a defect in the SCHAD enzyme of mitochondrial fatty acid oxidation. Diabetes. 2004;53:221-7. PubMed PMID: 14693719.

Nestorowicz A, Glaser B, Wilson BA, Shyng SL, Nichols CG, Stanley CA, Thornton PS, Permutt MA. Genetic heterogeneity in familial hyperinsulinism. Hum Mol Genet. 1998;7:1119-28. PubMed PMID: 9618169.

Nestorowicz A, Inagaki N, Gonoi T, Schoor KP, Wilson BA, Glaser B, Landau H, Stanley CA, Thornton PS, Seino S, Permutt MA. A nonsense mutation in the inward rectifier potassium channel gene, Kir6.2, is associated with familial hyperinsulinism. Diabetes. 1997;46:1743-8. PubMed PMID: 9356020.

Otonkoski T, Ammälä C, Huopio H, Cote GJ, Chapman J, Cosgrove K, Ashfield R, Huang E, Komulainen J, Ashcroft FM, Dunne MJ, Kere J, Thomas PM. A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland. Diabetes. 1999;48:408-15. PubMed PMID: 10334322.

Otonkoski T, Näntö-Salonen K, Seppänen M, Veijola R, Huopio H, Hussain K, Tapanainen P, Eskola O, Parkkola R, Ekström K, Guiot Y, Rahier J, Laakso M, Rintala R, Nuutila P, Minn H. Noninvasive diagnosis of focal hyperinsulinism of infancy with [18F]-DOPA positron emission tomography. Diabetes. 2006;55:13-8. PubMed PMID: 16380471.

Pinney SE, Ganapathy K, Bradfield J, Stokes D, Sasson A, Mackiewicz K, Boodhansingh K, Hughes N, Becker S, Givler S, Macmullen C, Monos D, Ganguly A, Hakonarson H, Stanley CA. Dominant form of congenital hyperinsulinism maps to HK1 region on 10q. Horm Res Paediatr 2013;80:18-27. PubMed PMID: 23859901.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016; 48:126-33. PubMed PMID: 26656846.

Sayed S, Langdon DR, Odili S, Chen P, Buettger C, Schiffman AB, Suchi M, Taub R, Grimsby J, Matschinsky FM, Stanley CA. Extremes of clinical and enzymatic phenotypes in children with hyperinsulinism caused by glucokinase activating mutations. Diabetes. 2009;58:1419-27. PubMed PMID: 19336674.

Sempoux C, Capito C, Bellanné-Chantelot C, Verkarre V, de Lonlay P, Aigrain Y, Fekete C, Guiot Y, Rahier J. Morphological mosaicism of the pancreatic islets: a novel anatomopathological form of persistent hyperinsulinemic hypoglycemia of infancy. J Clin Endocrinol Metab. 2011;96:3785-93. PubMed PMID: 21956412.

Stanley CA, Fang J, Kutyna K, Hsu BY, Ming JE, Glaser B, Poncz M. Molecular basis and characterization of the hyperinsulinism/hyperammonemia syndrome: predominance of mutations in exons 11 and 12 of the glutamate dehydrogenase gene. HI/HA Contributing Investigators. Diabetes. 2000;49:667-73. PubMed PMID: 10871207.

Thomas P, Ye Y, Lightner E. Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. Hum Mol Genet. 1996;5:1809-12. PubMed PMID: 8923010.

Tornovsky S, Crane A, Cosgrove KE, Hussain K, Lavie J, Heyman M, Nesher Y, Kuchinski N, Ben-Shushan E, Shatz O, Nahari E, Potikha T, Zangen D, Tenenbaum-Rakover Y, de Vries L, Argente J, Gracia R, Landau H, Eliakim A, Lindley K, Dunne MJ, Aguilar-Bryan L, Glaser B. Hyperinsulinism of infancy: novel ABCC8 and KCNJ11 mutations and evidence for additional locus heterogeneity. J Clin Endocrinol Metab. 2004;89:6224-34. PubMed PMID: 15579781.

License