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# Nonsyndromic Genetic Hyperinsulinism Overview

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

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## Summary

The purpose of this overview is to increase the awareness of clinicians regarding nonsyndromic genetic hyperinsulinism (HI) and its causes and management. The following are the goals of this overview.

### Goal 1

Describe the clinical characteristics of nonsyndromic genetic HI.

### Goal 2

Review the causes of nonsyndromic genetic HI and its differential diagnosis in a newborn with hyperinsulinemic hypoglycemia.

### Goal 3

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

### Goal 4

Inform (when possible) medical management of nonsyndromic genetic HI 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 nonsyndromic genetic HI.

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# 1. Clinical Characteristics of Nonsyndromic Genetic Hyperinsulinism

## Clinical Manifestations

Nonsyndromic genetic hyperinsulinism (HI) 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 newborn period, presenting symptoms may be nonspecific, including seizures, hypotonia, poor feeding, and apnea. Childhood-onset disease manifests in the first months or years of life. Children can present with an unprovoked seizure and/or hypoglycemia at the time of 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 onset can range from immediately after birth to late in childhood.

## Laboratory Features

In most individuals, HI 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.** Hyperinsulinism: Diagnostic Tests

| Specimen Type | Laboratory Test | Expected Result in Persons w/Hyperinsulinism |
|---|---|---|
| **Blood** | Insulin | Inappropriately elevated |
| | C peptide | Elevated |
| | Free fatty acids | Inappropriately low |
| | Beta-hydroxybutyrate | |
| | Acetoacetate | |
| | Lactic acid | Normal |
| | Carnitine | |
| | Growth hormone | Elevated due to hypoglycemia |
| | Cortisol | May be elevated due to hypoglycemia; can be normal if hypoglycemia is of short duration [1] |
| | $T_4$, $T_3$, TSH | Normal |
| | Ammonia | Elevated in persons w/hyperinsulinism-hyperammonemia syndrome; otherwise normal |
| **Urine** | Ketone bodies (at time of hypoglycemia) | Negative |
| | Reducing substances | |
| | 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 within 40 minutes following intravenous or intramuscular injection of 0.03 mg/kg glucagon, to a maximum of 1 mg, excludes a primary hepatic or metabolic defect and is virtually pathognomonic for HI.

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

**Severe disease.** In a newborn or young infant with severe disease that appears shortly after birth, the diagnosis of HI 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 plasma insulin concentration" is 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 interpreted as definitive. (2) The plasma glucose concentration that signifies symptomatic hypoglycemia is controversial, but measurement of plasma insulin should be done when plasma glucose is <50 mg/dL.

**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 inappropriately elevated insulin concentrations may be difficult to demonstrate convincingly. In these individuals, the following surrogate measurements of insulin action can be useful:

- Inappropriate hypoketonemia (plasma-free fatty acid concentration <1.5 mmol/L)

  Note: In the newborn period ketone production is impaired and the presence of low ketones should be considered together with the rest of the clinical and laboratory picture.
- A positive glucagon stimulation test (See **Glucagon stimulation test**.)
- A markedly elevated glucose requirement to prevent hypoglycemia (i.e., exogenous glucose requirements that may exceed 15 mg/kg/min [normal neonate: 5-8 mg/kg/min])

## Imaging

Fluorodopa F 18 positron emission tomography ($^{18}$F-FDOPA-PET) is recommended for the preoperative localization of focal lesions [De Leon et al 2024]. A newer nuclear medicine method using $^{68}$Ga-NODAGA-exendin-4 PET/CT has been tested and reported to be superior to $^{18}$F-FDOPA-PET but further evidence is needed [Boss et al 2022].

## 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 nonsyndromic genetic HI. A third histologic form ("atypical" or "mosaic") has also been described.

- **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. There is evidence for a role of transcription factor NKX2.2 in the development of mosaic HI [Han et al 2017]. Affected individuals in one family with a severe form of HI requiring pancreatectomy were found to have an *HK1* noncoding pathogenic variant resulting in inappropriate expression of *HK1* in the pancreas. The histology of the islets of Langerhans in specimens from affected individuals in this family was described as atypical, involving all islets in similar fashion but with different histologic appearance than the typical diffuse form [Wakeling et al 2022]. A molecular genetic study in pancreatic tissue identified postzygotic somatic pathogenic variants, an *ABCC8* dominant-acting variant, and mosaic paternal uniparental disomy of 11p15 in one individual with mosaic HI [Houghton et al 2020].

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 [Banerjee et al 2019]. 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 and, rarely, later develop ketotic hypoglycemia [Banerjee et al 2019].

# 2. Causes of Nonsyndromic Genetic Hyperinsulinism

Nonsyndromic genetic hyperinsulinism (HI) is the most common cause of persistent neonatal hypoglycemia and should be considered in every infant presenting with unexplained hypoglycemia. Pathogenic variants in many genes have been associated with nonsyndromic genetic HI; the precise number is difficult to report with accuracy because of overlap with syndromic HI [Zenker et al 2023]. Approximately 21%-55% of probands with nonsyndromic genetic HI do not have an identified molecular cause [Hewat et al 2022]. The diagnosis of nonsyndromic genetic HI in those without a molecular cause identified is established based on family history and lack of presence of an acquired cause of HI.

Table 2 lists genes associated with nonsyndromic genetic HI and genes associated with HI that may appear nonsyndromic in a newborn.

**Table 2.** Nonsyndromic Genetic Hyperinsulinism: Genes and Distinguishing Clinical Features

| Gene [1] | % of Nonsyndromic Genetic HI Attributed to Pathogenic Variants in Gene | MOI | Distinguishing Clinical Features |
|---|---|---|---|
| *ABCC8* [2] | 40%-45% [3] | AR | • Large for gestational age<br>• Severe refractory hypoglycemia in the 1st 48 hrs of life<br>• Respond only partially to diet or diazoxide & may require pancreatic resection<br>• 40% have focal form<br>• Diabetes may develop later in life<br>• Founder variants in Ashkenazi Jewish & Finnish populations [3] |
| | | AD | • Normal growth parameters at birth<br>• Present at age ~1 yr (range: 2 days-30 yrs)<br>• Respond to diet & diazoxide therapy; exceptions reported<br>• Variable penetrance |

*Table 2. continued from previous page.*

| Gene [1] | % of Nonsyndromic Genetic HI Attributed to Pathogenic Variants in Gene | MOI | Distinguishing Clinical Features |
|---|---|---|---|
| *GCK* | <1% [4] | AD | • Ranges from mild diazoxide-responsive hypoglycemia to severe, diazoxide-unresponsive hypoglycemia<br>• 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* | 42% of diazoxide-responsive HI w/ molecular diagnosis [5] | AD | • Mild-to-moderate hyperammonemia (1.5-4x upper limit of normal)<br>• Ammonia levels are not related to ambient glucose levels or to duration of fasting & appear to be benign.<br>• Mild hypoglycemia usually presents after neonatal period.<br>• May be assoc w/exquisite sensitivity to leucine challenge<br>• Most respond well to diazoxide; rarely, surgery is required to prevent recurrent hypoglycemia. |
| *HADH* | <1%<br>(4% of diazoxide-responsive HI w/ molecular diagnosis [5]) | AR | • ↑ urine 3-hydroxyglutaric acid & serum 3-hydroxybutyryl-carnitine<br>• Severe hypoglycemia after leucine administration<br>• Mild diazoxide-responsive hypoglycemia; severe hypoglycemia has been reported.<br>• Normal urinary 3-hydoxyglutaric acid & normal plasma acylcarnitine profile does not exclude the diagnosis. |
| *HK1* | 1 family [6] | AD | • Present before age 1 yr<br>• 40% present w/seizure<br>• Diazoxide responsive<br>• Failure to adequately suppress insulin secretion following oral glucose tolerance test or prolonged fasting<br>• Not leucine sensitive |
| *HNF1A* | 4% of diazoxide-responsive HI w/ molecular diagnosis [5] | AD | • Large for gestational age<br>• Mild diazoxide-sensitive hypoglycemia<br>• Hypoglycemia usually resolves in childhood.<br>• MODY3 develops in adolescence or adulthood. |
| *HNF4A* | 5% of diazoxide-responsive HI w/ molecular diagnosis [5] | AD | • Large for gestational age<br>• Mild diazoxide-sensitive hypoglycemia<br>• Hypoglycemia in neonatal & early infantile period<br>• Insulinopenic diabetes mellitus during adolescence |
| *INSR* | 24 persons from 9 families [7] | AD | • Postprandial hypoglycemia may be exacerbated by exercise.<br>• Variable age at onset & typical elevated insulin:C peptide ratio |
| *KCNJ11* [2] | 5% [8] | AR | • Large for gestational age<br>• Severe refractory hypoglycemia in 1st 48 hrs of life<br>• Affected infants usually respond only partially to diet or diazoxide therapy; may require pancreatic resection.<br>• 40% have focal form |
| | | AD | • Normal growth parameters at birth<br>• Present at age ~1 yr (range: 2 days-30 yrs)<br>• Respond to diet & diazoxide therapy; exceptions reported<br>• Variable penetrance |
| *PMM2* | 11 families [9] | AR | • Can present in infancy w/diazoxide-responsive HI w/o other apparent features<br>• Additional features of CDG type Ia become apparent over time, incl polycystic kidney disease, liver disease, liver cysts, & neurologic dysfunction |

*Table 2. continued from previous page.*

| Gene [1] | % of Nonsyndromic Genetic HI Attributed to Pathogenic Variants in Gene | MOI | Distinguishing Clinical Features |
|---|---|---|---|
| *SLC16A1* [10] | Unknown [10] | AD | • Hypoglycemia occurs during childhood or later.<br>• Severe hypoglycemia after exercise |
| *UCP2* | 2.4% of diazoxide-responsive nonsyndromic HI [11] | AD | • Mild diazoxide-responsive hypoglycemia<br>• Children reported w/hypoglycemia 4 hrs after glucose intake<br>• Role as monogenic cause of hypoglycemia has been questioned [12] |
| Unknown | 21%-55% [13] | NA | |

AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorders of glycosylation; HI = hyperinsulinism; MOI = mode of inheritance; NA = not applicable

*1.* Genes are listed alphabetically.

*2.* *ABCC8*- and *KCNJ11*-related nonsyndromic genetic HI are also known as $K_{ATP}$-HI.

*3.* De Franco et al [2020]

*4.* Li et al [2023]

*5.* Snider et al [2013]

*6.* Pinney et al [2013]

*7.* Sethi et al [2020]

*8.* Flanagan et al [2017]

*9.* Cabezas et al [2017]

*10.* Appears to be a rare cause of nonsyndromic genetic HI (3/153 in a Finnish series) [Nessa et al 2016, Männistö et al 2020]

*11.* Variable phenotype by age is reported, with children developing post-glucose-challenge hypoglycemia [Ferrara et al 2017].

*12.* Laver et al [2017] suggest, 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 the protein encoded by this gene is not proof of monogenic disease.

*13.* Hewat et al [2022]. The variable percentage of individuals with suspected nonsyndromic genetic HI without a molecular cause identified is likely affected by the method of molecular genetic testing.

## Differential Diagnosis of Nonsyndromic Genetic HI

**Genetic syndromes** in which HI may be a feature are listed in Table 3.

**Table 3.** Syndromes Associated with Hyperinsulinism

| Gene(s) / Locus | Disorder [1] | MOI |
|---|---|---|
| *ADK* | Adenosine kinase deficiency | AR |
| *ALG3* | ALG3-CDG | AR |
| *ALG6* | ALG6-CDG | AR |
| *CACNA1C* | *CACNA1C*-related disorders | AD |
| *CACNA1D* | PASNA syndrome (OMIM 615474) | AD |
| *CDKN1C*<br>11p15 [2] | Beckwith-Wiedemann syndrome | See footnote 2. |
| *CREBBP*<br>*EP300* | Rubinstein-Taybi syndrome | AD |
| *DIS3L2* | Perlman syndrome (OMIM 267000) | AR |
| *EIF2S3* | MEHMO syndrome (OMIM 300148) | XL |
| *FAH* | Tyrosinemia type I | AR |
| *FOXA2* | Syndromic hyperinsulinism | AD |

*Table 3. continued from previous page.*

| Gene(s) / Locus | Disorder [1] | MOI |
|---|---|---|
| *GPC3* | Simpson-Golabi-Behmel syndrome type 1 | XL |
| *HNF4A* | Fanconi renotubular syndrome (p.Arg76Trp) | AD |
| *HRAS* | *HRAS*-related Costello syndrome | AD |
| *INSR* | *INSR*-related severe insulin resistance syndrome | AR |
| *KCNQ1* | *KCNQ1*-related long QT syndrome | AD |
| *KDM6A*<br>*KMT2D* | Kabuki syndrome | AD<br>XL |
| *MEN1* | Multiple endocrine neoplasia type 1 | AD |
| *MPI* | MPI-CDG | AR |
| *NSD1* | Sotos syndrome | AD |
| *PGM1* | PGM1-CDG | AR |
| *PHOX2B* | Congenital central hypoventilation syndrome | AD |
| *PMM2* | PMM2-CDG | AR |
| *TRMT10A* | Syndromic hyperinsulinism (OMIM 616033) | AR |
| *YARS1* | *YARS1*-related disorder (OMIM 619418) | AR |
| 9p24 | 9p24 deletion syndrome [3] | AD |

AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorder of glycosylation; MOI = mode of inheritance; XL = X-linked

*1.* De Leon et al [2024]

*2.* Beckwith-Wiedemann syndrome (BWS) is associated with abnormal expression of imprinted genes in the BWS critical region. Abnormal expression of imprinted genes can be caused by a constitutional epigenetic or genomic alteration leading to an abnormal methylation pattern at 11p15.5 known to be associated with BWS; a 11p15.5 copy number variant; or a heterozygous maternally inherited *CDKN1C* pathogenic variant. Reliable recurrence risk assessment requires identification of the genetic mechanism in the proband that underlies the abnormal expression of imprinted genes in the BWS critical region.

*3.* Banerjee et al [2019]

**Acquired neonatal hyperinsulinemic hypoglycemia** may also be seen in:

- Infants of diabetic mothers (hypoglycemia typically resolves within days to weeks after birth but may require dietary glucose therapy with or without drug therapy with diazoxide);
- Transient hyperinsulinemic hypoglycemia of infancy, which typically responds well to diazoxide therapy and may occur after history of perinatal stress or asphyxia;
- Infants born to mothers taking certain drugs [De Leon et al 2024].

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

Establishing a specific genetic cause of nonsyndromic genetic hyperinsulinism (HI):

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

**Medical history.** There are a few points in the history that can help differentiate specific causes of nonsyndromic genetic HI. Hypoglycemia occurring postprandially, particularly after protein-rich meals, with relatively stable overnight glycemia and when combined with hyperammonemia would 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 nonsyndromic genetic HI. A history of severe hypoglycemia occurring after anaerobic exercise is suggestive of *SLC16A1*-related nonsyndromic HI. See Table 2 for additional findings that may suggest specific types of nonsyndromic genetic HI.

**Family history.** A three-generation family history should be taken, with attention to relatives with manifestations of nonsyndromic genetic HI and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing. Ethnic background can increase the probability of some genetic causes of nonsyndromic HI (e.g., *ABCC8* founder variant in Ashkenazi Jewish or Finnish individuals).

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

**Molecular genetic testing** approaches can include a combination of **gene-targeted testing** (multigene panel, serial single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

## Option 1

**A multigene panel** that includes some or all of the genes listed in Table 2 is most likely to identify the genetic cause of nonsyndromic genetic HI 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 family history and/or laboratory findings indicate that pathogenic variants in a particular gene are most likely (see Table 2).

- *ABCC8* sequence analysis can be considered first in individuals of Ashkenazi Jewish descent for the pathogenic founder variants NP_000343.2:p.Phe1387del or NM_000352.6:c.3989-9G>A.
- *ABCC8* sequence analysis can be considered first in individuals of Finnish descent for the pathogenic founder variants NP_000343.2:p.Val187Asp or NP_000343.2:p.Glu1506Lys.
- *GLUD1* sequence analysis can be considered first in individuals with elevated serum ammonia. Note: Sequencing of exons 6, 7, 10, 11, and 12 identifies virtually all pathogenic variants in *GLUD1*, although it is possible that causative variants occur in other exons as well.

## Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **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 Nonsyndromic Genetic Hyperinsulinism 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 rate of glucose infusion may be high, often greater than 15 mg/kg/min, and frequently requires central venous access. The definition of adequate glucose control has been the subject of discussion. A Pediatric Endocrine Society guideline recommends maintaining plasma glucose levels above 70 mg/dL (3.9 mmol/L) [Thornton et al 2015]. Rarely, slightly lower glucose levels may be tolerated [De Leon et al 2024]. During the initial treatment phase, a trial of enteral diazoxide should be initiated, and if adequate plasma glucose control is not achieved within 48 hours with an acceptable glucose infusion rate, intravenous glucagon should be used (given initially as 1 mg/24 hours mixed with 0.9% saline), later being replaced with octreotide initially at 10 mcg/kg/day as a continuous intravenous infusion.

Emergency treatment options for hypoglycemia must be available at all times in case of an unexpected hypoglycemic episode. During initial treatment, a second intravenous line should preferably be kept open in case of blockage of the first line in order to avoid a long wait while a new line is being prepared. If not already being infused, glucagon should also be ready and can be given rapidly by either intramuscular or subcutaneous injection or intranasal application.

## Long-Term Medical Management

During the next phase of treatment, the aim is to eliminate parenteral glucose requirements and involves a combination of medical therapies as described in Initial Treatment. Some individuals, particularly those with *GLUD1*-, *HADH*-, or *GCK*-related HI or autosomal dominant pathogenic variants in either *ABCC8* or *KCNJ11*, respond very well to medical therapy. Individuals with severe $K_{ATP}$-HI (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 following medications along with dietary intervention (that may 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 individuals with $K_{ATP}$-HI is extremely variable [Banerjee et al 2019]. The following is a summary of medications currently available.

- **Diazoxide** is currently the only FDA-approved medication for HI. It binds to the ABCC8 subunit of the $K_{ATP}$ channel and increases the channel's probability of being open, resulting in membrane hyperpolarization and inhibition of insulin release. Since this medication works at the site mutated in $K_{ATP}$-HI, it theoretically should not be effective for $K_{ATP}$-HI. However, diazoxide has been efficacious at high doses in some individuals with $K_{ATP}$-HI, particularly in those with focal disease. Therefore, diazoxide should be the first attempted medication intervention. 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 [De Leon et al 2024].
- **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. These medications are initially given intravenously as an aid to reduce glucose and prevent fluid overload. 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 these drugs also inhibit glucagon and growth hormone

secretion, thus impairing hepatic glucose production. Furthermore, the effect of these drugs typically declines over time with tachyphylaxis. Adjustment of dosage as needed (typically 10-15 µg/kg/day for octreotide but much higher doses have also been used) as well as the use of continuous subcutaneous injection with a portable pump enhances clinical efficacy [Banerjee et al 2019]. Long-acting analogs including long-acting release (LAR) octreotide and lanreotide can be used after the hypoglycemia becomes manageable and stable, usually after age three to four years. A multicenter retrospective study reported the major side effect that necessitated withholding treatment was elevated liver enzymes [van der Steen et al 2018].

- **Nifedipine,** which acts as an inhibitor of the voltage-dependent calcium channels present in the beta cell, inhibits insulin secretion by decreasing calcium influx. 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 [Güemes et al 2017].
- **Glucagon,** which increases hepatic gluconeogenesis, helps prevent hypoglycemia. It is highly effective when given intravenously in the initial treatment of neonatal hypoglycemia as mentioned above. It can also be administered chronically as replacement therapy alone or to counteract suppression by somatostatin analogs. However, its use is hampered by crystallization in tubing. A newer soluble form is experimentally available and is under trial [Banerjee et al 2019].
- **Glucocorticoids** induce resistance to endogenous insulin and correct the inadequate cortisol response sometimes seen in affected individuals. Their use in the treatment algorithm of nonsyndromic genetic HI is, however, very limited [Banerjee et al 2019].
- **Sirolimus** has been reported and used experimentally but is hazardous and is rarely used in clinical practice [Banerjee et al 2019].
- **Dietary intervention.** A major problem in children with HI is that they have to eat to avoid hypoglycemia. Consequently, eating becomes a chore instead of a pleasure-associated activity, thus precipitating food aversion. Furthermore, gastric motility is reduced and there is a tendency to vomit. In individuals with severe disease, feeding by gastrostomy tube is indicated to simplify the process of feeding and to provide access for emergency home treatment of hypoglycemia. Several options exist for dietary intervention to reduce hypoglycemia, which can be used alone or in combination:
  - Frequent high-carbohydrate feedings, including formula supplemented with glucose polymer
  - Nighttime continuous gastric drip containing glucose or glucose polymer
  - Background continuous glucose in gastric drip with intermittent supplementary feeds

## Surgical Management

In some individuals with severe HI, even the most aggressive medical management fails to consistently maintain plasma glucose concentration above 60-70 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:

- **Molecular genetic testing,** in certain circumstances, can be useful in differentiating focal from diffuse disease in *ABCC8*- or *KCNJ11*-related HI:
  - Identification of biallelic pathogenic variants (associated with autosomal recessive HI) or a heterozygous dominant-acting pathogenic variant (associated with autosomal dominant HI) is diagnostic of diffuse disease.
  - Identification of a heterozygous pathogenic variant (associated with autosomal recessive HI) 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.
  - Identification of a heterozygous pathogenic variant (associated with autosomal recessive HI) 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.

- **Fluorodopa F 18 positron emission tomography ($^{18}$F-FDOPA-PET)** is recommended for the preoperative localization of focal lesions [De Leon et al 2024]. Note: A newer nuclear medicine method using $^{68}$Ga-NODAGA-exendin-4 PET/CT is reported to be superior to $^{18}$F-FDOPA-PET but will need further study before being implemented widely [Boss et al 2022].
- **Intraoperative histologic evaluation of a pancreatic biopsy** in very experienced hands can be used to differentiate between diffuse nonsyndromic genetic HI 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. Use of intraoperative ultrasound to assist in localization has been suggested and shown to be another helpful modality after preoperative localization with $^{18}$F-FDOPA-PET. This modality was reported to reach 80% sensitivity and 100% specificity for detection of focal lesions [Bendix et al 2018].

Currently, long-term medical therapy is the recommended treatment for individuals with diffuse disease. When long-term medical therapy fails, extensive (80%-95%) pancreatic resection may be considered. This is only considered in exceptional, unresponsive cases, as such children remain at risk for persistent hypoglycemia postoperatively and have a high likelihood of developing insulin-requiring diabetes mellitus later in childhood [Banerjee et al 2019]. Individuals with focal disease can be cured by localized resection of the hyperplastic region, although surgery needs to be discussed and decided upon based on disease severity. As disease severity tends to improve over time, medical management remains an option in individuals with mild, medically manageable focal HI [Dastamani et al 2022].

## Surveillance

In persons with clinically mild disease, episodes of subtle, undiagnosed hypoglycemia can cause permanent brain damage. Therefore, close monitoring and treatment is just as critical in those with mild HI as it is in severe HI. 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 nonsyndromic HI 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 [De Leon et al 2024].

## Agents/Circumstances to Avoid

Prolonged fasting of any sort should be avoided.

## Pregnancy Management

Affected individuals who previously underwent near-total or subtotal pancreatectomy typically have insulin-requiring diabetes by the time they become pregnant. In these women treatment is the same as for individuals with preexisting diabetes of any cause. There is little published experience with pregnancy in individuals who were treated conservatively or who underwent limited pancreatectomy for focal nonsyndromic genetic HI. 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 nonsyndromic genetic HI 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 nonsyndromic genetic HI 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 Nonsyndromic Genetic Hyperinsulinism

*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

Recurrence risk assessment for family members of an individual with nonsyndromic genetic hyperinsulinism (HI) requires identification of the genetic cause of HI in the proband (see Table 4). Between 21% and 55% 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.

**Table 4.** Nonsyndromic Genetic Hyperinsulinism: Mode of Inheritance

| Phenotype | Mode of Inheritance | Genes |
|---|---|---|
| **Diffuse HI** | Autosomal recessive (biallelic pathogenic variants assoc w/autosomal recessive nonsyndromic HI) | *ABCC8* [1]<br>*HADH*<br>*KCNJ11* [1]<br>*PMM2* |
| | Autosomal dominant (heterozygous pathogenic variant assoc w/autosomal dominant nonsyndromic HI) | *ABCC8*<br>*CACNA1D*<br>*GCK*<br>*GLUD1*<br>*HK1*<br>*HNF1A*<br>*HNF4A*<br>*INSR*<br>*KCNJ11*<br>*SLC16A1*<br>*UCP2* |
| **Focal HI** | Heterozygous pathogenic variant assoc w/autosomal recessive nonsyndromic HI affecting paternal allele AND somatically acquired loss of heterozygosity of the maternal allele | *ABCC8*<br>*KCNJ11* |
| **Mosaic HI** | Pathogenic variant associated w/autosomal dominant HI | *ABCC8*<br>*GCK*<br>*HK1* |

HI = hyperinsulinism

*1.* Severe HI caused by autosomal recessive pathogenic variants in *ABCC8* or *KCNJ11* may be referred to as $K_{ATP}$-HI.

## Autosomal Recessive Inheritance of Diffuse HI – Risk to Family Members

**Parents of a proband**

- Both parents of an affected child are presumed to be heterozygous for an autosomal recessive HI-related pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an autosomal recessive HI-related pathogenic variant and allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- The heterozygous parents of a child with autosomal recessive diffuse HI are typically asymptomatic.

**Sibs of a proband**

- If both parents are known to be heterozygous for an autosomal recessive HI-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Sibs who inherit:
  - Biallelic pathogenic variants will be affected; however, manifestations may range from mild to severe in sibs with HI, and clinical presentation may range from immediately after birth to late in childhood.
  - An autosomal recessive HI-related *ABCC8* or *KCNJ11* pathogenic variant from the father and a normal allele from the mother are at a 1:540 risk for focal HI (see Risk to Family Members – Focal HI, **Sibs of a proband**) [Glaser et al 2011]. This risk reflects the likelihood of a somatically acquired "second hit" involving the 11p15.5 imprinted region on the maternal allele with resultant clonal expansion of cells with loss of heterozygosity and is expected to be independent of the specific pathogenic variant involved [Glaser et al 2011].
  - A normal allele from the father and an autosomal recessive HI-related *ABCC8* or *KCNJ11* pathogenic variant from the mother are asymptomatic and not at increased risk for focal HI.
  - An *HADH* or *PMM2* pathogenic variant from either parent and a normal allele from the other parent are asymptomatic and not at increased risk for focal HI.

**Offspring of a proband**

- Unless an affected individual's reproductive partner also has autosomal recessive HI or is heterozygous, offspring will be obligate heterozygotes for a pathogenic variant. The carrier frequency in the general population is approximately 1% or less; however, populations with founder variants and higher carrier frequencies have been reported.
  - *ABCC8* pathogenic variants p.Phe1387del and c.3989-9G>A are founder variants in the Ashkenazi Jewish population. In individuals of Ashkenazi Jewish descent, the carrier rate for the *ABCC8* pathogenic founder variant c.3989-9G>A is estimated at 1:83 [Zlotogora et al 2018].

- *ABCC8* pathogenic variants p.Val187Asp and p.Glu1506Lys are founder variants in the Finnish population [Männistö et al 2020]. The carrier rate of these founder variants is unknown.
- Heterozygous offspring of a male proband with *ABCC8*- or *KCNJ11*-related autosomal recessive HI are at risk of developing focal HI (see Risk to Family Members – Focal HI, **Offspring of a proband**).

**Other family members.** Each sib of the proband's parents is at a 50% risk of being heterozygous for an autosomal recessive HI-related pathogenic variant.

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

## Autosomal Dominant Inheritance of Diffuse HI – Risk to Family Members

**Parents of a proband**

- Some individuals with autosomal dominant diffuse HI inherited a causative pathogenic variant from an affected heterozygous parent.
- More typically, an individual with autosomal dominant diffuse HI has the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with autosomal dominant diffuse HI caused by a *de novo* pathogenic variant is estimated to be approximately 75%.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing for the pathogenic variant identified in the proband is recommended for the parents of the proband to evaluate their genetic status, inform recurrence risk assessment, and determine their need for surveillance. If a parent is found to have the autosomal dominant HI-related pathogenic variant, clinical testing for fasting and postprandial hypoglycemia is recommended (see Management, Surveillance). Note: A proband may appear to be the only affected family member because of failure to recognize the disorder in family members, reduced penetrance, early death of a parent before the onset of symptoms, or late onset of the disease in an affected parent. Therefore, *de novo* occurrence of an autosomal dominant diffuse HI-associated pathogenic variant in the proband cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the pathogenic variant.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

**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 possibility of parental gonadal mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, 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 autosomal dominant diffuse HI because of the possibility of reduced penetrance in a parent or the possibility of parental gonadal mosaicism.

**Offspring of a proband.** Each child of an individual with autosomal dominant diffuse HI 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.

## Focal HI – Risk to Family Members

**Parents of a proband**

- Focal HI is caused by a paternally inherited *ABCC8* or *KCNJ11* pathogenic variant associated with autosomal recessive HI in combination with a somatically acquired "second hit" involving the 11p15.5 imprinted region on the maternal allele and clonal expansion of the cells with the loss of the maternal allele. The father of an individual with focal HI is therefore presumed to be heterozygous for an *ABCC8*- or *KCNJ11*-related autosomal recessive HI pathogenic variant. Given the low risk for a person with such a pathogenic variant of having focal disease (estimated to be 1:540 due to a somatically acquired loss of heterozygosity of the maternal allele in a single cell [Glaser et al 2011]), the chance that both father and child are affected is less than 1:250,000. Thus, for practical purposes the father of an individual with focal HI does not have focal HI. (Note: *ABCC8* and *KCNJ11* pathogenic variants associated with autosomal dominant diffuse HI are not associated with focal HI.)
- Although no instances of focal HI caused by a *de novo* pathogenic variant on the paternally derived *ABCC8* or *KCNJ11* allele have been reported, it remains a possibility.
- Molecular genetic testing is recommended for the father of the proband to confirm that the father is heterozygous for the pathogenic variant identified in the proband and to inform recurrence risk assessment.

**Sibs of a proband**

- Sibs of a proband with focal HI have a 50% chance of inheriting the germline *ABCC8* or *KCNJ11* pathogenic variant from their father.
- Because focal HI manifests only when the inherited pathogenic variant is 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 HI in a sib with an inherited pathogenic variant is estimated to be 1:540 [Glaser et al 2011]. Sib recurrence of focal HI associated with a paternally inherited *ABCC8* pathogenic variant has been reported in one family to date [Ismail et al 2011].

**Offspring of a proband.** Each child of an individual with focal HI has a 50% chance of inheriting the germline *ABCC8* or *KCNJ11* pathogenic variant:

- Each child of a male proband with focal HI is at risk of developing focal HI. To develop focal HI, 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 HI to the offspring of a male proband with focal HI is 1:540 [Glaser et al 2011].
- The risk of diffuse HI in offspring depends on the genetic status of the proband's reproductive partner: offspring will have diffuse HI only if they inherit a pathogenic variant from both parents (see Related Genetic Counseling Issues, **Family planning**).
- The presence of focal HI in one sib does not rule out possible diffuse disease in another sib. Such an occurrence was reported in a consanguineous family in which both the mother and the father were heterozygous for an *ABCC8* pathogenic variant: one sib inherited only the paternal pathogenic variant and presented with focal disease; the other sib inherited biallelic *ABCC8* pathogenic variants and presented with diffuse disease [Valayannopoulos et al 2007].

**Other family members.** The sibs of the father of a proband with focal HI may also be heterozygous for an *ABCC8* or *KCNJ11* pathogenic variant. However, focal HI 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).

## Mosaic HI – Risk to Family Members

To date, all individuals with histologically proven mosaic HI [Houghton et al 2020, Boodhansingh et al 2022a, Boodhansingh et al 2022b] have had the disorder as the result of a somatic (postzygotic) pathogenic variant in *ABCC8*, *GCK*, or *GLUD1*. No epidemiologic or genetic evidence of inherited predisposition has been identified in individuals with mosaic HI.

**Parents of a proband.** The parents of an individual with a somatically acquired autosomal dominant HI-related pathogenic have not been reported to have genetic HI, nor would such a finding be expected given the postzygotic nature of mosaic HI-related genetic alterations reported to date.

**Sibs of a proband.** Given the somatic mutational mechanism of mosaic HI, the risk for an affected sib would be expected to be the same as in the general population.

**Offspring of a proband.** To date, there are no reported instances of vertical transmission of mosaic HI.

**Other family members.** The risk to other family members is presumed to be the same as that in the general population.

## Evaluation of Relatives at Risk

It is appropriate to clarify the clinical/genetic status of sibs of an individual with focal or diffuse HI 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 variant(s) 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(s) in the family are not known, careful glucose monitoring of newborns thought to be at risk based on the inheritance pattern should be undertaken (see Pregnancy Management), and parents should be aware of signs of hypoglycemia that would require investigation during childhood.

## Related Genetic Counseling Issues

**Family planning – autosomal recessive 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, are carriers, or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of known carriers and for the reproductive partners of individuals affected with genetic HI, particularly if both partners are of the same ancestry. *ABCC8* founder variants have been identified in the Ashkenazi Jewish and Finnish populations.

**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 and preimplantation genetic testing for a pregnancy at increased risk for diffuse HI (involvement of beta cells throughout the pancreas) 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 HI (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.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

## 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
  congenitalhi.org
- **MedlinePlus**
  Congenital hyperinsulinism

## Chapter Notes

### Author Notes

Dr David Gillis is active in treating children with hyperinsulinism and has been involved in clinical research, particularly focused on long-term outcomes of children with this disease. He would be happy to communicate with persons who have any questions regarding diagnosis and therapy of nonsyndromic or syndromic congenital hyperinsulinism. Email: dgillis@hadassah.org.il

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