Clinical Presentation and Management of Children With Diffuse and Focal Hyperinsulinism: A Review of 223 Cases

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Context: Congenital hyperinsulinism (HI) occurs in two distinct histologic forms: diffuse and focal. Distinguishing between them is essential because a pancreatectomy is curative for focal HI and palliative for diffuse HI.

Objective: The purpose of this study was to compare the presentations, treatment, and outcomes of diffuse and focal HI.

Design: A retrospective chart review of children who underwent pancreatectomy for hyperinsulinism from December 2004 through September 2012 was conducted.

Results: Based on pancreatic histology, 223 children were classified into 3 groups: diffuse (n = 97, 44%), focal (n = 114, 51%), and other (n = 12, 5%). Children with diffuse vs focal HI had significantly different mean gestational ages (38 vs 39 weeks, $P < .0005$) and birth weights (3963 vs 3717 g $P = .012$). Children with focal HI presented at an older age (0.3 vs 0 months, $P < .0005$) and more frequently with seizures (50 vs 25%, $P < .0005$). Children with diffuse HI had higher insulin levels during hypoglycemia (31.8 vs 12 μU/mL, $P < .0005$) and required higher glucose infusion rates (19.2 vs 16.1 mg/kg/min, $P = .002$). Children with diffuse HI had a median percent pancreactectomy of 98%, and postoperatively 41% required treatment for continued hypoglycemia. Children with focal HI had a median percent pancreatectomy rate of 27%, and 94% required no treatment after surgery.

Conclusions: Focal and diffuse HI present unique challenges, but the clinical differences between the 2 are subtle. Children with focal HI are at higher risk of delayed diagnosis and hypoglycemic seizures, but most are cured with surgery. In contrast, children with diffuse disease may be identified earlier, but face ongoing blood glucose abnormalities. **(*J Clin Endocrinol Metab* 98: E1786–E1789, 2013)**

Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in children. Inactivating mutations in the genes *ABCC8* and *KCNJ11*, encoding the 2 subunits of the β-cell ATP-sensitive potassium (K_{ATP}) channel, cause the most common and severe form of HI (K_{ATP}-HI) (1, 2). In most cases of K_{ATP}-HI, the mutation disrupts channel formation, and, therefore, diazoxide, a K_{ATP}-channel opener, fails to control the hypoglycemia (3). Given the risk of neurologic damage from hypoglycemia, most children with K_{ATP}-HI require a pancreatectomy.

There are 2 distinct histologic forms of HI, diffuse and focal. In diffuse HI, all β-cells in the pancreas are affected. Most commonly in diazoxide-unresponsive cases, diffuse

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Abbreviations: ^{18}F DOPA PET, 18-fluoro-L-3,4-dihydroxyphenylalanine positron emission tomography; K_{ATP}, ATP-sensitive potassium; HI, hyperinsulinism; LGA, large for gestational age.

HI is caused by biallelic recessive mutations in *ABCC8* or *KCNJ11* (4), but in a small percentage of cases, no mutations in these genes are found in the peripheral blood (5). The focal form of HI is characterized by a discrete lesion formed by hyperplastic islets or focal adenomatosis. A "two-hit" molecular mechanism is responsible for this form: first, a paternal recessive mutation in *ABCC8* or *KCNJ11*; and second, somatic loss of the maternal 11p15 region, compensated for by paternal uniparental disomy (6, 7). Infants with focal HI can be cured with surgical resection of the lesion, but this requires referral to a specialized center for an 18-fluoro-L-3,4-dihydroxyphenylalanine positron emission tomography (^{18}F DOPA PET) scan to identify and localize the lesion before surgery (3). In contrast, a pancreatectomy is palliative in children with diffuse disease; the majority will continue to have abnormal glucose metabolism after surgery (8). Given the different surgical outcomes, distinguishing between diffuse and focal disease early in the course of the disease is crucial. Genotyping is useful for distinguishing between the 2 forms with inheritance of a paternal recessive K_{ATP} mutation having a positive predictive value of 94% for focal disease (5). However, genetic testing may require 1 to 2 weeks, and it is not readably available in many countries.

The 2 forms of HI are assumed to be clinically indistinguishable from each other. We hypothesize that differences exist in the clinical presentation of children with diffuse and focal HI that can guide the clinician to consider early referral to a center with capabilities of finding and resecting focal lesions.

Materials and Methods

A retrospective chart review of children with hyperinsulinism who underwent a pancreatectomy between December 2004 (when ^{18}F-DOPA PET became available) and September 2012 at The Children's Hospital of Philadelphia was conducted. The diagnosis of hyperinsulinism was based on biochemical evidence of insulin excess at the time of hypoglycemia (plasma glucose <50 mg/dL): a detectable plasma insulin level and/or suppressed β-hydroxybutyrate and/or an inappropriate rise in glucose of >30 mg/dL after receiving 1 mg of glucagon. Classification by histologic type was made by pathologists experienced in the histologic features of HI and based on review of frozen pancreatic sections at the time of surgery and later confirmed by examination of permanent sections. Patients who underwent pancreatectomies for insulinomas were excluded. This study was reviewed and approved by the institutional review board of The Children's Hospital of Philadelphia.

Statistical analysis

Children with histologically confirmed diffuse or focal HI were included in the statistical analysis. Children with other histologic findings (n = 12) were excluded from the analysis. Baseline characteristics were summarized by standard descriptive summaries. Student *t* tests were used to compare means of normally distributed data (birth weight, critical sample glucose, and maximum glucose infusion rate). Mann-Whitney tests were used to compare mean ranks of nonparametric data (age at presentation, gestational age, critical sample insulin, critical sample β-hydroxybutyrate, critical sample free fatty acids, and percentage pancreatectomy). χ^2 or Fisher exact tests were performed to compare frequencies of categorical variables (sex, the presence of seizures, birth weight categorization, treatment with diazoxide, octreotide, and glucagon, and histologic characterization).

Results

Subjects

A total of 223 children underwent a pancreatectomy for congenital HI between December 2004 and September 2012. Of these, 51% were female, and the median age at pancreatectomy was 5 months (range 0.4–68.6 months). Histologic examination of the pancreas revealed diffuse HI in 44% (97 of 223) and focal HI in 51% (114 of 223). In 5% (12 of 223), histology was not consistent with either diffuse or focal disease. Of these 12 children, 6 had histology consistent with localized islet nuclear enlargement (9), 3 with Beckwith Wiedemann syndrome, and 3 with normal pancreatic tissue.

Initial presentation

Children with diffuse HI had significantly higher mean birth weights (3963 ± 757 vs 3717 ± 635 g, $P = .012$) and were more likely to be born large for gestational age (LGA) (76 vs 54%, $P < .0005$) than those with focal HI (Table 1). Children with diffuse HI were also more likely to be born at an earlier gestational age (38 weeks [range, 32–41 weeks] vs 39 weeks [range, 30–42 weeks], $P < .0005$). Children with focal disease were more likely to present at an older age (0.3 months [range, 0–15.7 months] vs 0 months [range, 0–35 months], $P < .0005$) and have seizures at presentation (50 vs 25%, $P < .0005$). Of the children with focal disease, 36% presented after 48 hours of life compared with 12% of children with diffuse disease ($P < .0005$). There were no significant differences based on sex or race.

Initial critical sample results

Children with diffuse disease had significantly higher median insulin concentrations (31.8 μU/mL [range, 0.6–299 μU/mL] vs 12 μU/mL [range, 1.8–202 μU/mL], $P < .0005$) than children with focal HI. Of the children in this cohort, 7% had an undetectable insulin level. There were no significant differences in plasma glucose, β-hydroxybutyrate, free fatty acids, or the proportion with an undetectable insulin level in the initial critical sample.

Table 1. Clinical Characteristics of Subjects with Diffuse and Focal HI

	Diffuse	Focal	*P* Value
Birth weight, g	3963 ± 757	3717 ± 635	<.0005
Gestational age, wk	38 (32–41)	39 (30–42)	.012
LGA birth weight, %	76	54	.001
Age at presentation, mo	0 (0–35)	0.3 (0–15.7)	<.0005
Seizures at presentation, %	25	50	<.0005
Glucose, mg/dL	35.8 ± 9.4	35.4 ± 9.0	.80
Insulin, μIU/mL	31.8 (0.6–299)	12 (1.8–202)	<.0005
β-Hydroxybutyrate, mM	0.10 (0–1.0)	0.11 (0–1.5)	.15
Free fatty acids, mM	0.27 (0.01–1.4)	0.48 (0.01–1.63)	.15
Treated with diazoxide, %	97	100	.10
Treated with octreotide, %	79	77	.70
Treated with glucagon, %	55	31	<.0005
Maximum glucose infusion rate	19.2 ± 7.8	16.1 ± 7.1	.002

Data are means ± SD or median (range).

Medical treatment before surgery

Before pancreatectomy, children with diffuse HI were more likely than those with focal HI to be treated with a glucagon infusion (55 vs 31%, $P < .0005$). They also required a significantly higher mean maximal glucose infusion rate (19.2 ± 7.8 vs 16.1 ± 7.1 mg/kg/min, $P = .002$). There were no significant differences in the proportion receiving diazoxide or octreotide treatment.

Genetics

Ninety-seven percent (94 of 97) of the children with diffuse HI and 98% (112 of 114) of those with focal HI had mutation analysis of *ABCC8*, *KCNJ11*, *GLUD1*, and *GCK*. Eighty-five percent (80 of 94 screened) of the children with diffuse HI were found to have a mutation in a K_{ATP} channel gene (75 with mutations in *ABCC8* and 5 in *KCNJ11*). One child with diffuse disease was found through pancreatic DNA analysis to have a postzygotic mutation in *GCK*, the gene encoding glucokinase. Ninety-eight percent (110 of 112 screened) of the children with focal HI were found to have a mutation in a K_{ATP} channel gene (99 with mutations in *ABCC8* and 11 in *KCNJ11*).

Surgery and outcomes

Children with diffuse HI had a significantly greater median percent pancreatectomy than those with focal HI (98% [range 15%–100%] vs 27% [range 1%–100%], $P < .0005$). At discharge after pancreatectomy, 94% (107 of 114) children with focal HI were euglycemic and required no treatment for blood glucose abnormalities. Five children with focal HI required treatment for continued hypoglycemia and 2 for hyperglycemia. In contrast, only 23% (22 of 97) of children with diffuse HI were euglycemic at discharge. Forty-one percent (40 of 97) required treatment for hypoglycemia, and 36% (35 of 97) required treatment for hyperglycemia.

Discussion

This is the largest study to date comparing the presentation, medical treatments, and surgical outcomes of children with diffuse and focal HI, in which all subjects are classified by histology of pancreas specimens. This study demonstrates differences in the clinical presentation of children with diffuse and focal HI. Compared with those with focal disease, children with diffuse disease appear to have more severe hyperinsulinism with higher birth weights, initial insulin concentrations, and glucose requirements, resulting in an earlier diagnosis than those with focal disease. Children with focal disease are identified later and, therefore, are more likely to have seizures due to hypoglycemia.

Despite demonstrating statistically significant differences in the presentations of diffuse and focal HI, the overlap in clinical parameters makes it difficult to clearly differentiate between the 2 types using clinical features only. Diagnosis must be based on clinical features plus the results of genetic testing and ^{18}F DOPA PET scan imaging. Although clinical features alone will not distinguish between the 2 types, they may guide clinicians as to which patients should have genetic testing performed as early as possible. An infant presenting with hypoglycemic seizures after the first several days of life should have genetic testing performed as soon as the diagnosis of HI is made. They may be more likely to have focal disease and will benefit from referral to a center with ^{18}F DOPA PET scan capabilities and expertise in the surgical management and pathology of HI. The high rate of cure after partial pancreatectomy for focal HI speaks to the importance of identifying children with focal HI and referring them to these centers.

Current guidelines for the management of neonatal hypoglycemia recommend screening of only at-risk infants,

including those born LGA (10). Only 50% of children with focal HI are born LGA compared with 75% of children with diffuse HI. Given that neonates with focal disease are less likely to be screened for hypoglycemia and that their hyperinsulinism may be less severe, more infants with focal HI are undiagnosed before discharge from the newborn nursery and are identified only when they present with hypoglycemic seizures weeks to months later. These findings suggest that the guidelines for neonatal hypoglycemia surveillance should be reconsidered.

A limitation of this study is its retrospective nature. In addition, the critical samples were collected at different institutions and processed at different laboratories with varying reference ranges. The vast majority of children referred to our institution are evaluated and treatment is initiated at other hospitals, so this limits our ability to gather uniform initial evaluation data. However, the rigorous and comprehensive presurgical evaluation of each patient with genetic analysis and an ^{18}F DOPA PET scan, intraoperative examination, and later confirmation of pancreatic histology strengthens this study. Nine percent of diffuse cases and 2% of focal cases lack identified genetic causes, highlighting the importance of continued research to identify new genetic defects.

In conclusion, this study demonstrates the subtle clinical differences in diffuse and focal hyperinsulinism and underscores the importance of distinguishing between the two forms. It also highlights the difficulties inherent in the care of children with these different forms. Whereas children with focal HI are at risk of delayed diagnosis, hypoglycemic seizures, and potentially longer exposure to hypoglycemia, most are cured with surgery. In contrast, although children with diffuse disease may be identified and treated earlier, they face on-going blood glucose abnormalities.

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