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Hypertrophic cardiomyopathy in neonates with congenital hyperinsulinism

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Abstract

Introduction—Hypertrophic cardiomyopathy (HCM) is a well-recognised complication in infants of diabetic mothers and is attributed to a compensatory increase in fetal insulin secretion. Infants with congenital hyperinsulinism have excessive prenatal and postnatal insulin secretion due to defects in pathways of insulin secretion (most commonly the K_{ATP} channel). HCM has been reported in a few neonates with hyperinsulinism, but its extent and risk factors for its development have not been evaluated.

Methods—Retrospective chart review of infants, age <3 months, with congenital hyperinsulinism managed by Children's Hospital of Philadelphia over a 3.5-year period.

Data—Gestational age, birth weight, hyperinsulinism form and treatments, echocardiogram results, cardiac/ respiratory complications.

Results—68 infants were included, 58 requiring pancreatectomy for diffuse (n=28) or focal (n=30) disease, 10 were diazoxide-sensitive. Twenty-five had echocardiograms performed. Ten had HCM, all of whom required pancreatectomy and eight of whom had confirmed ATP-sensitive potassium-hyperinsulinism. Subjects with HCM had younger gestational age 36(32, 38) than their surgical counterparts without HCM 38 (31.6, 43), p=0.02.

Discussion—HCM appears common in infants with severe hyperinsulinism. Routine echocardiogram and EKG of at-risk newborns should be considered. Fetal hyperinsulinism is the likely mediating factor for HCM in HI infants.

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a well-recognised comorbidity in infants of diabetic mothers.[1–4] Features include thickening of one or both of the ventricular walls including the interventricular septum; systolic and diastolic dysfunction may also be present. This cardiac complication in the infant of the diabetic mother has also been referred to as pathological ventricular hypertrophy to avoid confusion with the autosomal dominant form of congenital HCM.[5] While HCM in infants of diabetic mothers is reversible and frequently mild or asymptomatic, it can be severe and lead to fetal or neonatal death.[6–8] Most symptomatic infants require only supportive care with supplemental oxygen, but β-adrenergic blockers such as propranolol may be necessary to improve ventricular output.[9] Fetal hyperinsulinaemia in response to maternal hyperglycaemia has been implicated as the cause of HCM in infants of the diabetic mothers.[2]

Similar to infants of mothers with diabetes, infants with congenital hyperinsulinism have excessive insulin secretion in utero, are often large for gestational age (GA) and have hypoglycaemia within the first days of life. In infants with congenital hyperinsulinism this excess insulin secretion is not driven by hyperglycaemia. Instead, it arises from genetic defects in the pathways that regulate insulin secretion. The most common form of congenital hyperinsulinism is due to mutations in the genes encoding the β-cell ATP-sensitive potassium (K_{ATP}) channel composed of the sulfonylurea receptor 1 (SUR1) and the inwardly rectifying potassium channel (Kir6.2). These mutations may cause diffuse disease (in which all the β-cells of the pancreas are affected) or focal disease (in which an isolated, clonal expansion of β-cells hypersecrete insulin). Both forms are generally resistant to medical treatment with the K_{ATP} channel agonist, diazoxide, and require pancreatectomy.[10] Other forms of congenital hyperinsulinism that respond to diazoxide do not require surgical treatment.[10]

Given the similarities between infants with congenital hyperinsulinism and infants of diabetic mothers, the occurrence of HCM in infants with congenital hyperinsulinism is not unexpected. Moreover, the severe hypoglycaemia of congenital hyperinsulinism frequently necessitates the use of very large fluid volumes and fluid-retaining medications like diazoxide that could theoretically unmask otherwise asymptomatic HCM. Indeed, since the 1980's, HCM has been reported in five neonates with hyperinsulinism including two infants with transient, perinatal stress-induced hyperinsulinism.[11–14] This published literature likely underestimates the occurrence of HCM in infants with congenital hyperinsulinism, though. Recognition of HCM as a potential comorbidity in congenital hyperinsulinism cannot be overemphasised and is crucial for the safe management of these infants.

This study was undertaken to define the extent of cardiac complications in the congenital hyperinsulinism population and to identify potential risk factors that might be used for identifying at-risk patients and developing screening guidelines.

STUDY DESIGN AND METHODOLOGY

This study was conducted as a retrospective chart review of all infants less than 3 months of age treated at The Children's Hospital of Philadelphia for congenital hyperinsulinism over a 3.5-year period between February 2000 and May 2004. The Children's Hospital of Philadelphia (CHOP) is a major referral centre for infants and children with hypoglycaemia and hyperinsulinism. Infants were included if their hypoglycaemia was detected within the 1st week of life, the period when HCM presents, and if they were subsequently diagnosed with congenital hyperinsulinism. Infants were excluded if their hypoglycaemia was not recognised during the 1st week of life or if their hypoglycaemia was not due to congenital hyperinsulinism. The following data were collected: GA, birth weight (BW), age at

diagnosis of hypoglycaemia, age at diagnosis of congenital hyperinsulinism, medications (diazoxide, octreotide, glucagon, glucocorticoids) and their doses, form of hyperinsulinism (detailed below), K_{ATP} mutation site (SUR1, encoded by *ABCC8*, or Kir6.2, encoded by *KCNJ11*)—if known, maximum glucose infusion rate, plasma insulin concentration at the time of hypoglycemia (blood glucose, BG, ≤50 mg/dL), echocardiogram results, cardiac and respiratory complications, and treatments for cardiac/respiratory complications. For purposes of statistical analysis if the plasma insulin concentration was below the limit of assay detection it was defined as the value for the lower limit of detection. HCM was defined as presence of ventricular and/or interventricular wall thickness z-score>2 with or without ventricular dysfunction.[15]

Form of hyperinsulinism—Infants who required pancreatectomy were classified as surgical cases: either focal or diffuse depending upon final pathology. Infants who did not require pancreatectomy were classified as diazoxide-responsive congenital hyperinsulinism.

Statistical analyses

Mean and SD were used to summarise normally distributed continuous variables. Median and minimum/maximum were used to summarise continuous variables that were not normally distributed. Analysis of variance (ANOVA) or Kruskal-Wallis test, depending upon normality, was used to compare continuous variables among multiple groups. Student's t test or Wilcoxon rank sum test, depending upon normality, were used to compare continuous variables between HCM and non-HCM groups. Fisher's exact test was used to compare the presence/absence of cardiomyopathy among the forms of hyperinsulinism. Multivariable linear regression was used to identify risk factors for presence of cardiomyopathy. Analyses were conducted using Stata V.9.0 (Stata Corp., College Station, Texas, USA).

The study was approved by The Children's Hospital of Philadelphia Institutional Review Board.

RESULTS

A total of 68 infants were included in the study. Patient characteristics are summarised in table 1. Hypoglycaemia was detected in the majority of infants within the first day of life. The diagnosis of hyperinsulinism was made on average at age 3 weeks. As is typical for hyperinsulinism, insulin concentrations at the time of hypoglycaemia were modestly elevated, although many patients had levels below the limit of detection. On average, patients with congenital hyperinsulinism were treated with maximum effective doses of diazoxide (15 mg/kg/day) and octreotide (20 mcg/kg/day). Prior to their referral to CHOP, many patients with surgical hyperinsulinism (diffuse or focal) were treated with exogenous glucocorticoids.

Twenty-five patients had echocardiograms performed for various indications: murmur, cardiomegaly identified on chest radiograph, respiratory distress or arrhythmia. Ten of the 25 patients (40%) who had echocardiograms performed were identified as having HCM (table 2). Four had respiratory distress and required diuretics or propranolol; two required mechanical ventilation. All 10 were born large for GA and required pancreatectomy for either focal or diffuse hyperinsulinism after failing medical management with diazoxide and octreotide. Seven of the 10 had been treated with glucocorticoids for hypoglycaemia. Following treatment of hyperinsulinism and prior to discharge, HCM had improved/resolved in all 10 infants.

Echocardiograms (ECHO) were performed in 2 of 10 patients with diazoxide-sensitive hyperinsulinism, but neither had cardiomyopathy (table 1).

Potential risk factors for HCM were then sought. Since HCM was diagnosed only in patients who required pancreatectomy, patients with HCM were compared with those patients who required pancreatectomy but who were not suspected as having HCM (n=48). As shown in table 2, GA was younger in the HCM group (p=0.02). No other differences were found even after adjustment for GA but BW approached statistical significance (p=0.063).

As shown in table 3, among the 10 with HCM, 8 had genetic analysis and all had K_{ATP} channel mutations (seven had mutations in *ABCC8* and one had a mutation in *KCNJ11*). There were 15 patients who had ECHO performed but who did not have HCM, 14 of them had genetic analysis, 13 had K_{ATP} channel mutations (all of *ABCC8*).

DISCUSSION

In this study, symptomatic HCM was identified in approximately 15% (95% CI 6% to 23%) of infants with congenital hyperinsulinism. All 10 affected infants had the K_{ATP}-channel form of hyperinsulinism and ultimately failed medical management and required pancreatectomy. While the HCM eventually resolved in all cases, as shown in the illustrative case report it sometimes severely complicated management of the hyperinsulinism.

In infants of diabetic mothers, HCM is thought to arise from the effects of excess insulin. The finding of a very similar HCM in infants with congenital hyperinsulinism is consistent with a causal role for fetal hyperinsulinaemia in this cardiac abnormality. The mechanisms by which insulin causes ventricular hypertrophy have not been delineated, but the heart is an important insulin target, and expression of functional insulin receptors by the cardiomyocyte is comparable with that of other insulin-sensitive cells.[16] Downstream of the insulin receptor, glycogen synthase kinase-3β negatively regulates cardiac hypertrophy. Since expression of this enzyme is inhibited by insulin,[17] it is a potential mechanism for HCM in the hyperinsulinaemic fetus.

The frequency of asymptomatic cardiomyopathy in congenital hyperinsulinism is not known, but, as in infants of diabetic mothers, the cardiomyopathy may be unrecognised.[18] The clinical care required for these patients with congenital hyperinsulinism likely places them at risk for unmasking cardiac dysfunction. For instance, very high rates of intravenous fluid are frequently required to control hypoglycaemia in K_{ATP}-hyperinsulinism and can lead to fluid overload. Diazoxide, commonly used to treat hyperinsulinism, can cause fluid retention, thereby exacerbating an already fluid-overloaded state. In addition, despite their ineffectiveness in the treatment of hyperinsulinism, corticosteroids are often prescribed to infants with hypoglycaemia and have also been implicated in the development of HCM.[1920]

The finding of HCM only in patients requiring pancreatectomy in our series, suggests that the more severe the hyperinsulinism, the more likely is the occurrence of a disturbance in cardiomyocyte growth. However, the concentrations of insulin at the time of diagnosis failed to predict the presence of HCM. Similarly, BW did not predict presence of ventricular hypertrophy even though insulin is presumed to be the cause of the excessive fetal growth in infants with congenital hyperinsulinism, although it was suggested (p=0.063).

K_{ATP} channels play a key role in coupling the intracellular energy state to electrical activity and are expressed in most excitable tissues, including the heart. Under basal conditions, K_{ATP} channels are closed in cardiomyocytes and only activated with a lowered ATP/ADP ratio, as occurs in the setting of metabolic stress. By preventing excessive calcium entry and contraction, this channel activation is considered cardioprotective.[16] In contrast to pancreatic

β-cells which express Kir6.2 and SUR1, Kir6.2 and SUR2A are considered the physiologically relevant K_{ATP} channel subunits in the heart. Kir6.2 knockout mice are exercise intolerant and lack cardioprotection during ischaemia.[21] Mutations in the gene encoding SUR2 have been reported to cause a dilated cardiomyopathy.[22] Since (1) only one patient with HCM in our study had a *KCNJ11* mutation, (2) most patients with K_{ATP}-hyperinsulinism have *ABCC8* mutations and (3) there was no difference of K_{ATP} channel mutation between patients with HCM (8/10) vs patients who had ECHO performed but no HCM (13/15), impaired K_{ATP} channel activity in cardiomyocytes is unlikely to be responsible for ventricular hypertrophy in infants with congenital hyperinsulinism. Thus, fetal hyperinsulinism remains the likely mediating factor, as after treatment of hyperinsulinism, HCM had improved/ resolved in all infants.

This study has several limitations. Since echocardiography was performed only on symptomatic patients, the incidence of cardiomyopathy in infants with congenital hyperinsulinism is likely to have been underestimated. Nonetheless, 15% of all of the infants with congenital hyperinsulinism had HCM. The incidence was 17% (95% CI 7% to 25%) if only patients requiring pancreatectomy are included. How this figure compares with the incidence of cardiomyopathy in infants of diabetic mothers is difficult to determine as few studies have prospectively performed echocardiograms in infants of diabetic mothers. In a 1980 study, one-third of 45 infants of diabetic mothers had ventricular or septal hypertrophy;[23] however, this figure likely overestimates the incidence of HCM given that half of these infants were recruited based upon their admission to the neonatal intensive care unit. However, in a retrospective study of 87 infants of diabetic mothers who were admitted to a neonatal unit or whose mothers were seen in a perinatal unit, 12 had ventricular hypertrophy (13%), 2 of whom died.[5] Additionally, 7 of the 10 patients with HCM were treated with corticosteroid before transferring to CHOP, and corticosteroid might have played a role in HCM though they were treated for less than a month. While our sample size may be relatively small, it represents one of the largest cohorts of infants with hyperinsulinism in the world, and the results are likely generalisable to the congenital hyperinsulinism population.

In summary, our study shows that HCM is not uncommon in neonates with congenital hyperinsulinism. Infants with severe hyperinsulinism requiring pancreatectomy are at particular risk. Routine echocardiogram and electrocardiogram of the newborn infants with congenital hyperinsulinism, particularly in the setting of a murmur or respiratory difficulties, should be considered.

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What is already known on this topic

- Hypertrophic cardiomyopathy (HCM) is a well-recognised comorbidity in infants of the diabetic mothers, but has only been reported in five neonates with congenital hyperinsulinism thus far.
- Congenital hyperinsulinism is a disorder of hypoglycaemia arising from mutations in insulin secretion pathway genes, most commonly K_{ATP} channel mutations (SUR1 and Kir6.2).

What this study adds

- HCM is relatively common in neonates with congenital hyperinsulinism.
- Infants with severe hyperinsulinism requiring pancreatectomy are at particular risk.
- Routine ECHO and EKG for infants with congenital HI, particularly in the setting of a murmur or respiratory difficulties, should be considered.

Table 1

Patient characteristics mean (SD) (median and range for skewed data)

Hyperinsulinism form (n)	Gestational age (weeks) Median (min, max)	Birth weight (kg)**	#ECHO performed	Age hyperinsulinism diagnosis (days) median (min, max)	Plasma insulin during hypoglycaemia† (IU/ml) median (min, max)**	Maximum GIR (mg/kg/min)* Median(min, max)	Maximum diazoxide (mg/kg/day) Median (min, max)
Surgical							
Diffuse (28)	37 (32, 43)	4.1 (0.6)	12	8 (1, 114)	24 (2.9, 616)	17 (3, 40)	15 (0, 45)
Focal (30)	38 (31.6, 41)	3.7 (0.7)	11	8 (1, 118)	13 (0.6, 97)	13 (7.5, 39)	15 (0, 500)
Diazoxide-sensitive(10)	39 (35, 40)	3.7 (1.0)	2	12 (0, 67)	10 (6.2, 24)	8.5 (0, 50)	15 (5, 15)

*p=0.001.

**p<0.001 among the three groups (diffuse, focal, diazoxide-sensitive).

†Insulin at the time of hypoglycaemia (BG<2.8 mmol/l).

GIR, glucose infusion rate.

Table 2

K_{ATP} hyperinsulinism patients with hypertrophic cardiomyopathy (mean (SD) (median and range for skewed data)

Pt	ECHO	Treatment	HI-Form	BW (kg)**	GA (weeks)*	Insulin (IU/dl)	Maximum GIR (mg/kg/min)	Maximum diazoxide dose (mg/kg/day)	Maximum octreotide dose (mcg/kg/day)	GC
1	Concentric LVH	Supplemental O2	Diffuse	3.5	36	6.9	7	45	20	N
2	Severe HCM RVOT obstruction	propranolol	Diffuse	4.2	34	11.6	14	11	20	Y
3	HCM Thickened IVS	Mechanical ventilation w/ HFOV Lasix, propranolol	Diffuse	3.6	32	616	32	15	5	Y
4	Concentric LVH	Supplemental O2 lasix	Focal	4.2	36.5	97	30	15	15	Y
5	IVS hypertrophy	Mechanical ventilation, diuretics	Focal	4.6	38	22	38.7	15	40	Y
6	HCM, small PDA		Focal	4.4	36.9	1.5	20	10	21	Y
7	Mild LVH		Diffuse	4.5	38	31	16.6	15	20	N
8	BVH, hyperdynamic LV, moderate PDA		Focal	3.7	38	28	13	22	15	N
9	Mild LVH		Diffuse	4.0	33.7	92	23	15	20	Y
10	BVH		Diffuse	4.8	36	49	8.7	20	20	Y
Total				4.2 (0.4)	36 (32,38)	30 (1.5, 616)	26.4 (16.6, 50)	15 (10, 450	20 (5, 40)	7/10
Surgical (n=48)				3.9 (0.7)	38 (31.6, 43)	14 (0.6, 137)	25 (12.7, 40)	15 (0, 50)	20 (5, 343)	17/48

*p=0.02 HCM versus non-HCM surgical (focal and diffuse).

**p=0.063 after adjustment for GA.

Insulin at the time of hypoglycaemia (BG<2.8 mmol/l).

BW, birth weight; BVH, biventricular hypertrophy; GA, gestational age; GC, glucocorticoids; GIR, glucose infusion rate; HCM, hypertrophic cardiomyopathy; HFOV, high frequency oscillatory ventilation; IVS, interventricular septum; LVH, left ventricular hypertrophy; PDA, patent ductus arteriosus; SVT, supraventricular tachycardia.

Table 3

Gene analysis

	Patients	*ABCC8*	*KCNJ11*	Negative*	Not screen
HCM	10	7	1	0	2
Had ECHO but no HCM	15	13	0	1	1
Total patients had ECHO	25	20	1	1	3

*Negative means patients had genetic analysis, but negative for *ABCC8* and *KCJ11*.

HCM, Hypertrophic cardiomyopathy.