Persistent Hyperinsulinemic Hypoglycemia of Infancy : Experience at Siriraj Hospital

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Abstract

Background : Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of recurrent or persistent hypoglycemia in early childhood. Conventionally, pancreatectomy (Px) has often been recommended to control hypoglycemia. However, PHHI can be managed successfully by intensive medical treatment to avoid pancreatectomy.

Method : Data from 10 infants (8M, 2F) with PHHI were retrospectively analyzed.

Results : Eight patients (80%) developed symptoms within 72 hours after birth (early-onset). Six patients (60%) underwent 85 per cent-95 per cent Px due to failure of medical treatment. Two patients who underwent less than 95 per cent Px required second Px (97% and 99%). One patient developed permanent diabetes mellitus and malabsorption. Hypoglycemia could be successfully managed by medication alone in four patients (40%). Of these, three patients had early-onset neonatal hypoglycemia. Medication could be discontinued in three patients (75%).

Three of ten patients (30%) had delayed development. Pancreatectomies and/or the diagnosis of PHHI were made late for these patients. One of these three children also developed epilepsy.

Conclusions : Patients with PHHI frequently require pancreatectomy which commonly results in long-term complications especially diabetes mellitus and malabsorption. Our data suggest that PHHI can be managed successfully with an intensive medical regimen even in patients with early-onset hypoglycemia. Although medical management is very laborious for the family and physician, it should be applied until euglycemia is accomplished. Moreover, the early diagnosis of PHHI and the successful hypoglycemic control are very necessary to prevent permanent neurologic sequelae.

Key word : PHHI, Pancreatectomy

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Hypoglycemia is the most common metabolic disorder in the first year of life, with potentially devastating consequences in causing severe brain damage if not recognized and treated promptly. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of recurrent or persistent hypoglycemia in early childhood[1]. It is characterized by inadequate suppression of insulin secretion in the presence of severe, recurrent, fasting hypoglycemia.

It is now clear that mutations in at least four different genes responsible for the ability of the β-cell to regulate insulin secretion are associated with PHHI. These genes are the sulphonylurea receptor (SUR1), the potassium channel (Kir6.2), glutamate dehydrogenase (GDH), and glucokinase (GK)[2].

Medical treatment of PHHI consists of intravenous glucose infusion, frequent carbohydrate feedings and drugs administration to control insulin secretion. Diazoxide and octreotide are the first line medications[3]. Glucagon can be used temporarily to control hypoglycemia. Nifedipine, a calcium channel blocker has recently been used with some success in children with severe hyperinsulinism. Unfortunately, diazoxide and octreotide were not always available initially for our patients. Hydrocortisone was then used to control hypoglycemia when diazoxide was not available. Pancreatectomy is indicated for children who fail medical treatment. Repeated pancreatectomies are sometimes necessary to control hypoglycemia. Major complications of pancreatectomy are diabetes mellitus and pancreatic exocrine insufficiency.

The authors report their experience with the long-term outcome following medical treatment with and without pancreatectomy in children with PHHI who were treated at the Department of Pediatrics, Siriraj Hospital, Mahidol University.

PATIENTS AND METHOD

In the 15-year period from 1985-2000 10 patients with PHHI (8 boys and 2 girls) were treated. Seven patients were referred from other hospitals in Thailand. The diagnosis of PHHI was based on inappropriately elevated insulin concentrations at the time of hypoglycemia (insulin/glucose ratio $\geq$ 0.3), absence of ketone bodies in urine, a glycemic response > 30 mg/dl to glucagon in the face of hypoglycemia. Growth hormone and cortisol deficiencies were excluded by appropriate testings.

Medical management included 1. Intravenous glucose infusion to maintain euglycemia and oral feeds every three hours 2. If glucose requirement was > 15 mg/kg/min, add (a) Hydrocortisone 5 mg/kg every 12 hours if diazoxide was not available initially (b) Glucagon 5-10 mcg/kg/h continuous iv infusion (c) Octreotide 5-10 mcg every 6-8 hours subcutaneously (d) Diazoxide 5-15 mg/kg/day in 3-4 divided oral doses. In addition, nifedipine 0.25-2.5 mg/kg/day in 3 divided oral doses was used in one patient.

If hypoglycemia persisted despite aggressive medical treatment, pancreatectomy was performed to enable better control of blood sugar with or without medication.

Pertinent data of all patients are listed in Table 1, 2 and 3.

RESULTS

Clinical and laboratory data are presented in Tables 1-3. All the symptoms developed early after birth except two patients who presented at 2 and 4 months of age. All early onset patients were large for their gestational ages but the late onset patients were not. Six patients presented with seizures.

Three patients (patient no. 4, 6, 9) were referred to our hospital more than two weeks after the initial presentation.

The diagnosis for all patients was straightforward. Insulin/glucose ratios in all patients were > 0.3 during hypoglycemic episodes. Multiple blood samples were needed in some patients to obtain one with insulin/glucose ratio > 0.3.

Six patients (60%) underwent 85 per cent-95 per cent pancreatectomy due to failure of medical treatment (Table 2). Two patients (patient no. 9 and 10) required a second operation with 97 per cent and 99 per cent pancreatectomy. One patient (patient no. 1) did not receive diazoxide before surgery. One patient (patient no. 9) received nifedipine. Of these patients (6 patients) who underwent pancreatectomy, two patients required diazoxide for 7 and 16 months post-operatively. One patient did not require any medication to control hypoglycemia whatsoever. However, one patient (patient no. 10) developed diabetes mellitus right after 2nd pancreatectomy which required chronic insulin administration. This patient was later diagnosed with malabsorption at 8 months after the 2nd pancreatectomy. Two patients remained on hydrocortisone after pancreatectomy. Hydrocorti-

Table 1. Clinical and laboratory data of patients with PHHI.

Patient no.	Sex	Age of onset	Case origin	GA (weeks)	BW (grams)	Symptoms	Insulin (μU/ml)	Glucose (ml/dl)	Insulin/glucose ratio
1	Male	day 1	Referred	40	4,180	Hypoglycemia/seizure	Unavailable	Unavailable	Unavailable
2	Male	day 1	Referred	40	4,590	Hypoglycemia/seizure	16.69	33	0.5
3	Male	day 1	Siriraj H	38	4,950	Hypoglycemia	38.38	25	1.5
4	Male	4 months	Referred	40	2,800	Hypoglycemia/seizure	25.25	22	1.1
5	Male	day 3	Referred	40	4,500	Hypoglycemia	11.07	23	0.5
6	Male	day 2	Referred	32	2,750	Hypoglycemia/seizure	58.7	20	2.9
7	Female	day 1	Siriraj H	40	4,830	Hypoglycemia	46.5	41	1.1
8	Male	day 1	Siriraj H	33	2,760	Hypoglycemia	17.8	21	0.8
9	Female	day 2	Referred	40	4,000	Hypoglycemia/seizure	126	20	6.3
10	Male	2 months	Referred	40	3,200	Hypoglycemia/seizure	50	<50	>1.0

GA = gestational age, BW = birth weight, Siriraj H = Siriraj Hospital

sone was gradually tapered to prevent adrenal insufficiency secondary to prolonged glucocorticoid administration. One of these two patients was on nifedipine before and after pancreatectomy.

Hypoglycemia could be managed by medication alone in four patients (40%, Table 3). Three patients required diazoxide for 10, 11 and 23 months. One patient was still on diazoxide to control hypoglycemia at the last follow-up.

All but three had normal development. One (patient no. 10) also developed epilepsy at age 4 7/12 years.

DISCUSSION

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of hypoglycemia in early childhood. The biochemical diagnosis of PHHI depends upon demonstrating increased insulin secretions at the time of hypoglycemia. The diagnosis in all of the presented patients was straightforward. The insulin: glucose ratios were ≥0.3 in all of them. However, it is known that serum insulin concentrations are not consistently elevated and cannot be relied upon to make the diagnosis of PHHI. Instead, one must demonstrate increased insulin action with suppressed ketones and a glycemic response to glucagon at the time of hypoglycemia[2].

Four patients (40%) could be successfully managed with intensive medical treatment (Diazoxide in four patients, Octreotide in three patients). Three patients had very early neonatal hypoglycemia. Both diazoxide and octreotide are first line drugs for the treatment of PHHI[3]. Hydrocortisone was used initially for two patients due to the unavailability of diazoxide. Diazoxide is one of the most effective drugs for controlling hyperinsulinemic hypoglycemia. It primarily activates the K_{ATP} channel through sulphonylura receptor (SUR1) to inhibit insulin secretion. Octreotide is a long-acting somatostatin analog. It activates β-cell potassium channels to inhibit insulin secretion. Octreotide can be given by continuous intravenous or subcutaneous infusion or by intermittent subcutaneous injection. Glucagon was used in three patients. It is usually used as a temporizing agent to control hypoglycemia. It antagonizes insulin action by mobilizing hepatic glycogen stores, thereby decreasing the glucose requirement of a patient with hyperinsulinism[2].

Interestingly, three patients with very early neonatal hypoglycemia were diazoxide-responsive.

Table 2. Long-term outcome following pancreatectomy in 6 patients with PHHI.

Pat no.	Age of onset	Age at Dx	Surgery	Age at surgery	Pre-operative medication	Post-operative medication	Age at last visit (years)	Follow-up duration after surgery (years)	Outcome
1	day 1	12 days	90% Pancreatectomy	26 days	Glucagon, Octreotide	Diazoxide for 16 months	5.6	5.5	Well, good in school
3	day 1	2 days	95% Pancreatectomy	18 days	Hydrocortisone, Glucagon, Diazoxide, Octreotide	None	5	5	Well, good in school
5	day 3	6 days	95% Pancreatectomy	27 days	Hydrocortisone, Glucagon, Diazoxide,	Diazoxide for 7 months	1.4	1.3	Normal development
6	day 2	8 months	95% Pancreatectomy	13.7 months	Hydrocortisone, Diazoxide, Octreotide,	Cortone acetate till present	5	3.9	Delayed motor development
9	day 2	2 months	90% and 97% Pancreatectomy	15 and 17 months	Diazoxide, Octreotide, Nifedipine	Nifedipine and cortef till present	1.6	0.2	Delayed speech development
10	2 months	2.25 months	85% and 99% Pancreatectomy	10, 21 months	Hydrocortisone, Diazoxide	Insulin	12	10.3	Delayed development Diabetes mellitus Malabsorption Seizure

Table 3. Long-term outcome of 4 patients with PHHI who were managed with medication alone.

Pat. No.	Age of onset	Age of Dx	Initial medication	Prolonged medication	Age at last visit (years)	Outcome
2	day 1	8 days	Glucagon, Diazoxide, Octreotide	Diazoxide for 23 months	3.7	Normal development
4	4 months	6.7 months	Glucagon, Diazoxide, Octreotide	Diazoxide till present	6.3	Well, good in school
7	day 1	7 days	Hydrocortisone, Glucagon, Diazoxide, Octreotide	Diazoxide for 10 months	1.3	Normal development
8	day 1	7 days	Hydrocortisone, Diazoxide	Diazoxide for 11 months	1.1	Normal development

Contrary to most reports of diazoxide unresponsiveness in patients with early onset neonatal hypoglycemia who have recessive mutations in the sulphonylurea receptor (SUR1) and the potassium channel (Kir6.2) genes commonly found in other populations (2), PHHI in Thai patients may have different mutations in hyperinsulinism-associated genes. Further molecular genetic studies will provide more definite answers.

Six patients (60%) underwent 85 per cent-95 per cent pancreatectomy. Five of six patients developed hypoglycemia within the first few days of life (early-onset). Our data suggest that early onset PHHI is associated with more severe hyperinsulinism which are diazoxide-unresponsive and thus require pancreatectomy. Genetic studies of the sulphonylurea receptor (SUR1) and Kir 6.2 genes are necessary for these patients. The diazoxide-unresponsiveness in these patients might be attributed to the inability of diazoxide to act on the K_{ATP} channel. Previous data suggest that 95 per cent pancreatectomy is the optimal resection for early-onset PHHI , whereas partial pancreatectomy (65-80%) may be adequate for late-onset PHHI(4). The two patients who required 2nd pancreatectomy underwent less than 95 per cent pancreatectomy initially. This finding supports that less than 95 per cent pancreatectomy might not be adequate for early-onset PHHI. Shilyansky et al. reported that near-total pancreatectomy controlled hypoglycemia in 97 per cent of patients, 95 per cent pancreatectomy was associated with 33 per cent persistent hypoglycemia and < 85 per cent pancreatectomy resulted in 50 per cent cure rate(5).

One patient who underwent pancreatectomy did not receive diazoxide. The pancreatectomy might have been avoided if diazoxide had been available for the patient.

Although the ultimate goal of surgery is cure, pancreatectomy may only decrease β-cell mass sufficiently to allow more effective medical management(2) like in the presented patients who required diazoxide or nifedipine to control hypoglycemia after surgery. Nifedipine was used effectively to control hypoglycemia after pancreatectomy in one patient. It has been used with some success in children with severe hyperinsulinism but experience with its use is limited(6,7). Nifedipine is thought to antagonize voltage dependent calcium channels to inhibit insulin secretion. The present data suggest that nifedipine might be a good alternative treatment of PHHI.

Permanent diabetes mellitus can occur immediately post-operatively from a large resection (2) like in one patient who underwent 99 per cent pancreatectomy. This patient also developed pancreatic exocrine insufficiency. Shilyansky et al reported that 86 per cent of patients who underwent near-total pancreatectomy developed diabetes within three years of surgery(5). None of the presented patients who underwent 90-97 per cent pancreatectomy developed diabetes after 0.2-5.5 years post-pancreatectomy. However, long term follow-up is mandatory in these patients. Late-onset diabetes can be manifested during puberty when an antiinsulin state unmasks decreased β-cell reserve.

PHHI can cause significant morbidity if not recognized or carefully treated. Neurologic sequelae of hypoglycemia include seizures and permanent

brain damage. The degree, duration and frequency of hypoglycemia needed to cause permanent brain damage are not well defined, but with at least 20 per cent of children with hyperinsulinism beset with significant brain damage(8). From the presented data, three of ten children (30%) had delayed development. One of the three patients had seizure disorder. Interestingly, pancreatectomies were performed late after the initial presentation (8-15 months) and/or the diagnosis of PHHI was made late in these particular patients (8-15 months). Therefore, the importance of prompt and complete intervention of PHHI cannot be overemphasized.

Molecular genetic studies of PHHI-associated genes in patients with early onset PHHI who are diazoxide responsive and those who are diazoxide unresponsive are necessary. These might give better understanding of the pathophysiology of the diasease and lead to more effective medical intervention.

In conclusion, the presented data suggest that although early-onset PHHI commonly requires pancreatectomy (no less than 95% pancreatectomy is recommended), However, early-onset PHHI can be managed successfully with an intensive medical regimen to avoid potential complications of pancreatectomy especially diabetes mellitus. Although medical management is very laborious for the family and physician, it should be applied until euglycemia is accomplished. Moreover, the early diagnosis of PHHI and the successful hypoglycemic control are very necessary to prevent permanent neurologic sequele. Molecular genetic studies of hyperinsulinism-associated genes will definitely give a better understanding of the disease.

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ประสบการณ์การรักษาภาวะน้ำตาลต่ำอย่างต่อเนื่องในเด็กเนื่องจากระดับอินสุลินในเลือดสูง ที่โรงพยาบาลศิริราช

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ภาวะน้ำตาลต่ำอย่างต่อเนื่องในเด็กเนื่องจากระดับอินสุลินในเลือดสูง (PHHI) เป็นสาเหตุที่พบบ่อยที่สุดของภาวะน้ำตาลต่ำในวัยเด็ก โดยปกติการควบคุมระดับน้ำตาลที่ต่ำมักอาศัยการผ่าตัดเอาตับอ่อนออก (Pancreatectomy) แต่อย่างไรก็ตามภาวะน้ำตาลต่ำจาก PHHI สามารถรักษาได้โดยใช้การรักษาด้วยยาเพียงอย่างเดียว ข้อมูลจากผู้ป่วยเด็ก 10 ราย (ชาย 8, หญิง 2) ได้ถูกนำมาวิเคราะห์ ผู้ป่วย 8 ราย (80%) มีน้ำตาลต่ำภายใน 72 ชั่วโมงหลังคลอด ผู้ป่วย 6 ราย (60%) ได้รับการผ่าตัดเอาตับอ่อนเป็นออกปริมาณ 85–95% เนื่องจากการรักษาด้วยยาไม่สามารถควบคุมระดับน้ำตาลได้ โดยผู้ป่วย 2 ราย ต้องได้รับการผ่าตัดตับอ่อนออกเป็นครั้งที่ 2 ในปริมาณ 97 และ 99% ผู้ป่วย 1 รายมีภาวะแทรกซ้อนหลังการผ่าตัด ได้แก่เบาหวานและการดูดซึมอาหารผิดปกติ มีผู้ป่วยถึง 4 ราย (40%) ที่ได้รับการรักษาภาวะน้ำตาลในเลือดต่ำโดยการใช้ยารักษาแต่เพียงอย่างเดียว โดยในจำนวนนี้ 3 รายมีภาวะน้ำตาลต่ำในช่วง 72 ชั่วโมงแรกหลังคลอด โดยสามารถหยุดยาได้ในผู้ป่วย 3 รายจาก 4 ราย

ผู้ป่วย 3 รายจาก 10 ราย (30%) มีพัฒนาการผิดปกติ เป็นที่น่าสังเกตว่าผู้ป่วยเหล่านี้ได้รับการวินิจฉัยและหรือได้รับการผ่าตัดตับอ่อนออกล่าช้า ผู้ป่วย 1 รายใน 3 รายต่อมาได้รับการวินิจฉัยเป็นโรคลมชัก

พบว่าในอดีตบ่อยครั้งที่ผู้ป่วยที่มีภาวะ PHHI ต้องได้รับการผ่าตัดเอาตับอ่อนออกเพื่อจะรักษาภาวะน้ำตาลต่ำโดยผู้ป่วยจะมีผลแทรกซ้อนจากการผ่าตัดได้บ่อย โดยเฉพาะเบาหวานและการดูดซึมอาหารผิดปกติ จากผลการศึกษานี้ชี้ให้เห็นว่าการใช้ยาโดยไม่ผ่าตัดเอาตับอ่อนออกสามารถรักษาภาวะ PHHI ได้แม้ในผู้ป่วยที่มีน้ำตาลต่ำในช่วง 72 ชั่วโมงแรกหลังคลอด การรักษาด้วยยา ควรนำมาใช้กับผู้ป่วยที่มีภาวะ PHHI ถึงแม้ว่าจะเป็นภาระที่หนักสำหรับครอบครัวและแพทย์ และที่สำคัญก็คือการวินิจฉัยและการรักษาภาวะน้ำตาลต่ำใน PHHI ที่รวดเร็วมีความจำเป็นอย่างยิ่งในการป้องกันผลแทรกซ้อนของระดับน้ำตาลที่ต่ำโดยเฉพาะต่อระบบประสาท

คำสำคัญ : ภาวะน้ำตาลต่ำอย่างต่อเนื่องในเด็กเนื่องจากระดับอินสุลินในเลือดสูง, การผ่าตัดเอาตับอ่อนออก

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