Persistent Hyperinsulinemic Hypoglycemia of Infancy: Experience With 28 Cases

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■ Twenty-eight infants with persistent hyperinsulinemic hypoglycemia of infancy (PHHI) were seen during a 10-year period. There were 13 males and 15 females. Their age at time of presentation ranged from a few hours to 6 months. Consanguinity was reported in 20 cases (71.4%). One family had two affected siblings and two affected cousins, another had three affected siblings and one affected cousin, and three others had lost siblings because of hypoglycemia and seizures. The primary clinical presentation was jitters and seizures in association with hypoglycemia. The diagnosis was suspected when the therapeutic glucose requirement was found to be more than 12 mg/kg/min and also when there was a good response to glucagon after exclusion of metabolic and storage diseases. A high insulin-to-glucose ratio was noted for all patients. Twenty-two had near-total (90%) pancreatectomy; the result was excellent in all but four, who required supplemental medical therapy. Five patients were treated medically, and one patient's family refused treatment. Twelve patients sustained moderate to severe brain injury before referral. There were no deaths, and only one patient had evidence of malabsorption after the pancreatectomy. PHHI correlates well with consanguinity and family history. Clinical awareness is essential to permit early diagnosis and prompt medical and supportive therapy. Early surgery is recommended in the majority of cases if permanent brain damage is to be avoided. Near-total pancreatectomy provides the best surgical outcome, with little morbidity and no mortality.
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INDEX WORDS: Hyperinsulinism, persistent hyperinsulinemic hypoglycemia, infancy; pancreatectomy.

PERSISTENT hyperinsulinemic hypoglycemia of infancy (PHHI) is an uncommon disorder.[1,2] The disease is usually diagnosed in the neonatal period or later in infancy, but a number of cases have also occurred in adults.[3] Laidlaw (1938) coined the term nesidioblastoma to describe the disorder, but PHHI is now considered to be a more acceptable descriptive title.[4,5] The majority of reported cases of PHHI are sporadic. However, the familial incidence has been recognized recently, suggesting an autosomal-recessive inheritance.[5-9] We report our experience with 28 cases of PHHI treated during a 10-year period, with emphasis on clinical presentation, family history, and surgical management.

MATERIALS AND METHODS

Twenty-eight infants with PHHI were treated at King Faisal Specialist Hospital and Research Centre and King Khalid University Hospital, Riyadh, Saudi Arabia, between 1984 and 1993. The medical records of the patients were reviewed with respect to age, gender, clinical presentation, family history, management, and outcome. Glycogen storage disease, metabolic disorders, and hormonal disorders were excluded. The diagnosis was based on a persistently low blood glucose level (<2.3 mmol/L), negative urinary ketone bodies and reducing substances, a positive glucagon stimulation test result, and a high insulin-to-glucose ratio. The diagnostic workup is shown in Table 1.

RESULTS

The series included 13 males and 15 females who presented from a few hours to 6 months of age. Nineteen (68%) presented during the first week of life. There was a history of consanguinity in 20 cases, the parents being first-degree cousins in 13 and second-degree cousins in 7. One family had two affected siblings and two affected cousins, another had three affected siblings and one affected cousin, and three other families reported that siblings had died because of hypoglycemia and seizures. The clinical presentation (Table 2) was manifestation of a low blood glucose level, which was a consistent finding. Results of serum cortisol, growth hormone, and metabolic studies were normal for all patients. The ratio of insulin (μIU/mL) to glucose (mg/dL) ranged from 0.4 to 2.7 (mean, 0.87; normal, <0.3). Abdominal ultrasonography showed the pancreas to be normal in 19 cases. Fourteen also had computerized tomography, which also showed a normal pancreas. In two patients, a small incidental liver hemangioma was detected.

All patients initially were managed with a high oral or parenteral glucose diet. The glucose requirement ranged from 8 to 30 mg per kilogram of body weight per minute (mean, 16.8 mg). It was noted that an early presentation was usually associated with a higher glucose requirement. The aim of medical management, which was attempted in all patients, was to achieve and maintain a normal blood glucose level, for which purpose diazoxide (dose, 10 to 20 mg/kg/d) was the most commonly used drug. In

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Table 1. Diagnostic Tests During Hypoglycemia (Blood Glucose < 2.8 mmol/L)

Test	Frequency	Result
Urinary ketone bodies	Once	Negative
Urinary reducing substances	Once	Negative
Serum		
Insulin	Three times, at different periods	Elevated
C-peptide		Elevated
Serum		
Cortisol	Once	Normal
Growth hormone	Once	Normal
Metabolic screen	Once	Normal
Glucagon stimulation (0.03 mg/kg intravenously)	Once	Positive increase in glucose (>30 mg/dL)

severe cases, corticosteroids and glucagon were used to temporarily increase the blood glucose level. Somatostatin analogue was used in one patient for persistent hypoglycemia after pancreatectomy. In five patients, medical management was successfully continued with oral diazoxide and frequent feeding. At the 1-year follow-up, two patients were off medications but required frequent feeding, and three were maintained on diazoxide. The family of one patient refused medical and surgical therapy, and the ultimate outcome of this child is not known.

Twenty-two patients had near-total (90%) pancreatectomy, the indication for surgery being failure of medical therapy (20) or poor family compliance (2). The operation was performed through a transverse abdominal incision, with the dissection commencing at the tail of the pancreas. Bipolar electrocoagulation was used for the small blood vessels, and the splenic vessels were protected. The entire pancreas, including the uncinate process, was mobilized. The tail and body of the pancreas were resected together with partial resection of the head and the uncinate process to protect the common bile duct. Approximately 10% of the pancreatic tissue was left behind, which is considered to be enough to prevent pancreatic exocrine insufficiency or the development of diabetes mellitus.[10-12] There was no operative mortality, and only two patients had superficial wound infection. Table 3 shows the outcome for surgical patients. Histological examination of the pancreatectomy specimen showed diffuse islet cell hyperplasia in 19 patients and focal microadenoma in three patients.

Table 2. Clinical Presentation (n = 28)

Symptom	No. of Patients	%
Seizures	22	78.5
Jitters	12	42.8
Hunger	5	17.8
Sweating	5	17.8
Apneic spells	3	10.7
Lethargy	2	7.1

NOTE. Six patients had severe and six had mild to moderate brain damage at the time of presentation.

DISCUSSION

PHHI is considered to be uncommon; Vane et al reported only four cases among 92 infants and children with pancreatic problems.[13] The condition is even less common among adults.[3] The large experience reported herein may be attributable to the high rate of consanguinity in Saudi Arabia, genetic predisposition, as well as a selective referral base. The familial incidence reported by others was also noted in our series, indicating an autosomal-recessive mode of inheritance.[5-8] An important lesson learned from our series is that the late referrals were associated with a high rate of brain injury (12 of the 28 cases). It is clear that early diagnosis is mandatory, followed by aggressive medical and/or surgical treatment, to avoid the ravages of hypoglycemia. Early referral to centers experienced in the management of such cases is therefore recommended.[6,10]

Medical therapy was initiated in all our patients with PHHI, which included a high-glucose diet and diazoxide. In addition, somatostatin analogue was given to one patient. Corticosteroids and glucagon were used for temporary relief of hypoglycemia. Medical therapy was effective mainly in patients who presented after the neonatal period. Diazoxide was the drug of choice and was accepted by the parents, despite the complication of hirsutism. We did not encounter any cardiac complications, presumably because we used oral diazoxide and kept the dose below 20 mg/kg/d.[14,15] Two of our patients on diazoxide were in remission and off therapy.

Surgery in the form of subtotal or near-total pancreatectomy appears to be the most effective definitive treatment of PHHI, especially for neonates with

Table 3. Surgical Result (n = 22)

Response or Complication	Number (%)	Remark
Good	16 (72.7)	Off medication, normal diet
Borderline	6 (27.3)	Frequent meals (6)
		Diazoxide (4)
		Somatostatin (1)
Pancreatic insufficiency	1 (4.5)	—
Diabetes mellitus	0	—

NOTE. The follow-up period was 4 months to 6 years (mean, 2 years) for 21 patients; one was lost to follow-up.

severe hypoglycemia.[10,11] Two years (mean) after pancreatectomy there were no cases of diabetes mellitus. However, one case from the early part of the series showed evidence of mild pancreatic insufficiency and may have had a more extensive pancreatic resection than the subsequent cases.

Radiological assessment of the pancreas (ultrasonography and/or computerized tomography) did not prove useful for the first 19 patients with PHHI. Therefore, in the last nine we did not undertake any specific radiological investigations.

Our data confirm that familial PHHI is common in communities having a high rate of consanguinity. Clinical awareness of the condition is essential to ensure early diagnosis, followed by aggressive medical therapy and early surgery (in severe cases) to avoid permanent brain damage.

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