Persistent hyperinsulinemic hypoglycemia of infancy: long-term follow-up after surgical treatment

F.N. Wahid, M. Al Onazi, A. Al Rawaf, M. Al Muhaidly, A. Al Otaibi and J. Al Hudhaif

Aim **The aim of this study was to investigate the long-term outcome of six children with persistent hyperinsulinemic hypoglycemia of infancy (PHHI) after pancreatectomy who have been followed since 1990 at the Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia.**

Patients and methods **Data from six patients were retrospectively analyzed from chart review. PHHI was diagnosed on the basis of having high-insulin levels and low-glucose levels and a high insulin-to-glucose ratio. Lactate, pyruvate, ammonia, and urinary organic acid levels were recorded and tandem mass spectrometry screening was performed. The patients were assessed radiologically by MRI of the brain and by ultrasound examination of the abdomen. Patients who failed medical therapy underwent near-total pancreatectomy.**

Results **Hypoglycemic convulsion was the most common presenting complaint. None of the patients responded to medical treatment and thus underwent surgery. Two patients still had hypoglycemic episodes after surgery, requiring medical treatment. However, they underwent subsequent surgery because of unresponsiveness to medical therapy. Three patients developed diabetes. None of them had malabsorption, and two patients later developed epilepsy.**

Conclusion **The earlier the age at diagnosis, the better the neurological outcome. Delayed surgery might be associated with higher risk of development of diabetes. Near-total (90–95%) pancreatectomy is the treatment of choice for PHHI not responsive to medical treatment.** ***Ann Pediatr Surg*** **7:123–125** © **2011 Annals of Pediatric Surgery.**

Annals of Pediatric Surgery 2011, **7**:123–125

Keywords: Near-total pancreatectomy, outcome, persistent hyperinsulinemic hypoglycemia of infancy

Department of Pediatric Surgery, Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia

Correspondence to Mohammed Al Onazi, Consultant, Department of Pediatric Surgery, Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia
Tel: +966 505466625; fax: +966 505466625; e-mail: alonazy_99@yahoo.com

Received 14 June 2011 **Accepted** 24 July 2011

Introduction

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), formally known as nesidioblastosis, is a glucose metabolic disorder characterized by hypoglycemia and inappropriate secretion of insulin [1]. The disease includes focal and diffuse forms, both of which have a similar clinical presentation. Its incidence in the general population is one of 50 000 live births [2], but in areas with high-consanguineous unions the incidence may be as high as one of 2500 live births [3]. The familial form may be caused by autosomal recessive or dominant defects in the sulfonylurea receptor gene [4], the potassium inward-rectifying receptor (Kir6.2) gene [5], the glutamate dehydrogenase gene [6], or the glucokinase gene [7]. The chromosome involved is 11p14-15.1. Babies with PHHI run a high risk of severe neurologic damage secondary to severe hypoglycemia unless immediate and adequate steps are taken [8]. These steps should include high-glucose infusion and medical treatment with diazoxide, octreotide (somatostatin analog), and nifedipine. However, surgery should be considered if medical treatment is not successful [9].

Patients and methods

We have retrospectively analyzed the charts of six children at Riyadh Military Hospital, Riyadh. They were diagnosed with PHHI in 1990. Four children (three girls and one boy) belonged to the familial group and two were in the sporadic group. The disease was diagnosed on the basis of high-insulin levels, low-glucose levels, and a high insulin-to-glucose ratio. All patients underwent assessment of lactate, pyruvate, and ammonia levels, as well as growth hormone, cortisol, and thyroid hormones. Urinary organic acid screening and tandem mass spectrometry were also performed. Radiological assessment was made by MRI of the brain and by ultrasound examination of the abdomen. Our management policy was to maintain blood sugar level at more than 70 mg/dl (3.88 mmol/l). Medical therapy included diazoxide (maximum dose: 25 mg/kg/day) and octreotide (maximum dose: 40 mg/kg/day), glucagon injection (as required) and intravenous glucose infusion (15 mg/kg/min). If medical therapy as initial management failed (lack of response), the patient was subjected to near-total (90–95%) pancreatectomy. Surgery was performed by an open technique. Blood sugar was monitored frequently postoperatively. If the patient remained hypoglycemic (blood glucose < 2 mmol/l), medical therapy was started. Glucose infusion was continued and adjusted according to blood sugar levels.

Results

All babies were born after full-term pregnancies. The birth weights ranged from 3.3 to 3.8 kg (median: 3.6 kg). There were six patients (four girls and two boys). One family had four affected children. At the time of this study, patient age ranged from 6 months to

1687-4137 © 2011 Annals of Pediatric Surgery DOI: 10.1097/01.XPS.0000405090.49368.85

Table 1 Patients' age, birth weight, and age at presentation, diagnosis, and surgery

	Familial cases				Sporadic cases	
	1	2	3	4	5	6
Age at last follow-up visit	17 years	8 years	7 years	5 years	12 years	6 months
Age at presentation	5 days	First day	First day	First day	6 days	2 days
Birth weight	3.3 kg	3.8 kg	3.8 kg	3.6 kg	3.5 kg	3.3 kg
Age at diagnosis	75 days	First day	First day	First day	60 days	45 days
Age at surgery	6 months	1 month	1 month	1 month	3 months	3 months

Table 2 Type of surgery and long-term outcomes

	Familial cases				Sporadic cases	
	1	2	3	4	5	6
Type of surgery	70%	90% followed by 95%	90%	95%	95%	95% followed by 98%
Hypoglycemia	No	Following first surgery	No	No	No	Following first surgery
Age at development of diabetes	10 years	None	None	1 year	10 years	None
Exocrine insufficiency	No	No	No	No	No	No
Neurological abnormality	Epilepsy	Epilepsy	None	None	None	None

17 years (median age: 8 years). Age at diagnosis ranged from a few hours after birth to 2½ months. Age at surgery ranged from 1 to 6 months (median: 3 months) (Table 1).

Hypoglycemic convulsion was the most common presenting complaint. All patients had inappropriately elevated levels of insulin during episodes of hypoglycemia ranging from 12 to 125 mU/ml. The insulin-to-glucose ratio was high for all patients, and all patients required glucose infusion rate greater than 15 mg/kg/min. All patients had normal growth hormone, cortisol, and thyroid hormone levels. Lactate, pyruvate, and ammonia levels were also normal. Urinary organic acid screening and tandem mass spectrometry screening were negative for all patients. MRI of the brain was significant for two patients who later developed epilepsy. Ultrasound examination of the abdomen was unremarkable. All patients were started on diazoxide, octreotide, and glucose infusion. In addition, glucagon was given (as required) PRN. The medical treatment was considered a failure when patients, despite undergoing maximum treatment, had hypoglycemic episodes. All patients required surgery after failure of medical treatment. Three patients underwent 95% pancreatectomy, two patients underwent 90% pancreatectomy, and one patient underwent 70% pancreatectomy. Two patients (one who underwent 90% pancreatectomy and another who underwent 95% pancreatectomy) had repeated hypoglycemic episodes that required medical treatment after surgery, which later required a second surgery. Obvious overgrowth of the remaining pancreas was observed during the second surgery of the patient who underwent 95% pancreatectomy, which was performed 4 months after the first surgery.

Three patients developed diabetes: two at 10 years of age, including one who had 70% pancreatectomy, and one at 1 year of age. None of the patients had exocrine insufficiency or developmental delay. Two patients developed epilepsy later (Table 2). There was no mortality. All patients continue to be followed at the clinic. Histology for all patients revealed diffuse nesidioblastosis.

Discussion

We have presented the clinical outcome of six patients with PHHI who underwent surgery after failure of medical treatment with a mean follow-up of 8.25 years. Most of the cases are sporadic. However, in our series we had four patients from the familial group (66.6%) and two from the sporadic group (33.2%). Insulin-dependent diabetes developed in three out of six (50%) treated children (two at the age of 10 years and one at the age of 1 year). Other investigators have found that diabetes develops in 56% of children having near-total pancreatectomy [9]. We found that older age at surgery leads to greater risk of diabetes, in agreement with previous studies [10]. This finding relating age at surgery and development of diabetes needs confirmation with larger case series before they can be generalized. Two children were hypoglycemic after surgery, requiring medical treatment, which later required second surgery. One patient underwent 90% pancreatectomy during the first surgery and the other underwent 95% pancreatectomy. Overgrowth of the remaining pancreas was observed in one patient who underwent 95% resection. Postpancreatectomy pancreatic regrowth in four infants with PHHI has also been documented in other studies [9,11]. Postpancreatectomy regrowth is well documented in experimental models [12]. The patient who underwent 70% pancreatectomy (the first case in our series) was operated upon by a general surgeon who was covering the service of pediatric surgery at that time. This might explain the underestimation of the actual percentage of the pancreatectomy in this case, which did well postoperatively.

All patients were developmentally normal and two patients (33.3%) were diagnosed with epilepsy after a

few years as compared with 64% of patients with developmental delay in another series [13], possibly associated with delayed treatment.

In our cases, age at diagnosis ranged from a few hours after birth to 2½ months (median age, few hours). This is because most of our patients were from the same family and had been admitted soon after birth to the Neonatal Intensive Care Unit for workup.

Conclusion

The earlier the age at diagnosis, the better the neurological outcome. Delayed surgery might be associated with higher risk of development of diabetes. Pancreatectomy 90–95% is the treatment of choice for PHHI not responsive to medical treatment.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Aynsley Green A. Nesidioblastosis of the pancreas in infancy. *Dev Med Child Neurol* 1981; **23**:372–379.
2 Bruining GJ. Recent advances in hyperinsulinism and the pathogenesis of diabetes mellitus. *Curr Opin Pediatr* 1990; **2**:758–765.
3 Mathew PM, Young JM, Abu Osba YK, Mulhern BD, Hammoudi S, Hamdan JA, *et al*. Persistent neonatal hyperinsulinism. *Clin Pediatr (Phila)* 1988; **27**:148–151.
4 Thomas PM, Cote GJ, Wohllk N, Haddad B, Mathew PM, Rabl W, *et al*. Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. *Science* 1995; **268**:426–429.
5 Thomas P, Ye Y, Lightner E. Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. *Hum Mol Genet* 1996; **5**:1809–1812.
6 Stanley CA, Lieu YK, Hsu BY, Burlina AB, Greenberg CR, Hopwood NJ, *et al*. Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N Engl J Med* 1998; **338**:1352–1357.
7 Glaser B, Kesavan P, Heyman M, Davis E, Cuesta A, Buchs A, *et al*. Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med* 1998; **338**:226–230.
8 Schwitzgebel VM, Gitelman SE. Neonatal hyperinsulinism. *Clin Perinatol* 1998; **25**:1015–1038.
9 Shilyansky J, Fisher S, Cutz E, Perlman K, Filler RM. Is 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate? *J Pediatr Surg* 1997; **32**:342–346.
10 Jack MM, Greer RM, Thomsett MJ, Walker RM, Bell JR, Choong C, *et al*. The outcome in Australian children with hyperinsulinism of infancy: early extensive surgery in severe cases lowers risk of diabetes. *Clin Endocrinol* 2003; **58**:355–364.
11 Schonau E, Deeg KH, Huemmer HP, Akcetin YZ, Bohles HJ. Pancreatic growth and function following surgical treatment of nesidioblastosis in infancy. *Eur J Pediatr* 1991; **150**:550–553.
12 Sumi S, Tamura K. Frontiers of pancreas regeneration. *J Hepatobiliary Pancreat Surg* 2000; **7**:286–294.
13 Ismail D, Werther G. Persistent hyperinsulinaemic hypoglycaemia of infancy: 15 years' experience at the royal children's hospital (RCH), Melbourne. *J Pediatr Endocrinol Metab* 2005; **18**:1103–1109.