OBJECTIVE: To describe the clinical, surgical, biochemical, radiological and electrophysiological features of 43 Saudi children with persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) who have been followed since 1983.

METHODS: Data from 43 patients were retrospectively analysed. PHHI was diagnosed on the basis of high intravenous glucose requirement, high insulin to glucose ratio, negative urinary ketones and normal tandem mass spectrometry. The patients were assessed radiologically by brain magnetic resonance imaging and/or computed tomography and electrophysiologically by brain stem auditory evoked potential, visual evoked response and electroencephalogram. Patients who failed medical therapy received near total pancreatectomy.

RESULTS: The patients were severely hypoglycaemic and intolerant to fast. Hypoglycaemic convulsion was the most commonly presenting complaint. Eighteen patients were developmentally delayed and 14 of them had brain atrophy. All patients, except nine, did not respond to medical treatment and underwent surgery. Four pancreatectomized patients developed diabetes and two had malabsorption. One baby had 180 cm resection of gangrenous bowel most likely secondary to octreotide. No common bile duct injury was encountered. One patient was treated medically during childhood and developed diabetes and gained weight during adolescence.

CONCLUSION: PHHI is a relatively common and serious disease among Saudi children. Early intervention is necessary to avoid neurological damage in patients who are severely hypoglycaemic and unresponsive to medical therapy. Surgically and probably medically treated patients are at a high risk of developing diabetes, which could be the natural outcome of this disease. Care and spending time during surgery to visualize the common bile duct help in avoiding its injury. [Asian J Surg 2006;29(3):207–11]

Key Words: hyperinsulinaemia, hypoglycaemia

Introduction

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI), formally known as nesidioblastosis, is a glucose metabolic disorder characterized by profound hypoglycaemia and inappropriate secretion of insulin. The disease includes focal and diffuse forms, both have a similar clinical presentation but different molecular mechanism. Its incidence in the general population is 1/50,000 live births, but in areas with high inbreeding such as the Kingdom of Saudi Arabia, the incidence may be as high as 1/2,500, where most of the cases are familial. This familial form
may be caused by recessive or dominant defects in the sulfonylurea receptor (SUR1) gene, potassium inward rectifying receptor (Kir6.2) gene, glutamate dehydrogenase gene or the glucokinase gene.

Babies with PHHI run a high risk of severe neurological damage secondary to severe hypoglycaemia unless immediate and adequate steps are taken. These steps should include high glucose infusion and medical treatment with diazoxide and octreotide (somatostatin analogue). The diffuse form is usually sensitive to medical treatment. Elective surgery (near or subtotal pancreatectomy) or resection of the focal lesion has to be performed as soon as possible, particularly in cases where medical treatment is not successful.

Patients and methods

We retrospectively analysed the records of 43 children (26 girls and 17 boys) (King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia) who were diagnosed with PHHI between 1983 and 2004. The disease was diagnosed on the basis of high intravenous glucose infusion ≥ 12 mg/kg/minute, insulin to glucose ratio ≥ 0.3, 30 minute-glucose increment ≥ 30 mg/dL (1.67 mmol/L) in response to 0.5 mg intramuscular glucagon, negative urine ketones and normal blood spot acylcarnitine profile determined by tandem mass spectrometry (MS). All patients had assessment of growth hormone, adrenocorticotropic hormone (ACTH), insulin and cortisol levels. Patients were also assessed radiologically by brain magnetic resonance imaging (MRI), computed tomography (CT) or both. Patients were evaluated electrophysiologically by electroencephalogram, brain stem auditory evoked response and visual evoked response. Echocardiogram was performed in patients who were suspected to have cardiac disease. Our management policy was to maintain blood sugar level at ≥ 70 mg/dL (3.88 mmmol/L). Medical therapy included diazoxide (maximum dose, 25 mg/kg/day) and octreotide (maximum dose, 40 mg/kg/day) as well as intravenous glucose infusion. If medical therapy as initial management failed (lack of response or development of side effects), the patient was subjected to near total pancreatectomy (85–95%). The surgical technique was usually done by an upper abdominal incision and through the cologastric omentum. The pancreas was usually dissected off the pancreas using a bipolar diathermy. The large vessels that cross into the pancreas were ligated and tied by 3/0 silk. At the uncinate process, dissection was carried out carefully by exploring and mapping of the mesenteric vessels and portal vein. Identification of the common bile duct prior to dissection at the head of the pancreas is mandatory and different techniques have been used in order to identify the common bile duct, including identification of the common bile duct by dissection in the hepatoduodenal ligament and following the duct down behind the duodenum, insertion of tube through the gallbladder down through the cystic duct and common bile duct, cholangiogram and infusion of saline through the gallbladder with clamping of the first and third parts of the duodenum after clamping of the pancreatic head and prior to resection to confirm duct patency (distension of the duodenum indicates patency of the duct). Transection of the pancreatic head was done using endo GIA (US Surgical, Norwalk, CT, USA). Few cases and redo cases have been done by transection with knife and closure of the pancreatic resection margin with 3/0 silk suture using figure of 8, penrose drain was usually left behind. One case was done by laparoscopic technique. Postoperatively, patients were fed within 48–72 hours. Blood glucose was monitored frequently postoperatively. If the patient remained hypoglycaemic (blood glucose ≤ 2 mmol/L), a second cycle of medical therapy (diazoxide, octreotide) was started. Glucose infusion was continued and adjusted according to the baby’s blood sugar.

Results

All babies were the result of full-term pregnancies except for five preterm babies. The birth weights ranged from 2.5 to 4.5 kg (median, 3.5 kg). The consanguinity was very high in our group of patients. Seventeen parents were first-degree cousins, eight were second-degree cousins and five were far relatives. One family had seven affected children and three families had two siblings with PHHI. The current patient age ranged from 3 months to 19 years (median, 5 years). The age of the first documented hypoglycaemia ranged from a few hours to 1 year (median, 1 day), and the age at which the diagnosis was made ranged from 10 days to 3 years (median, 2 months). Age at surgery ranged from 1 month to 4 years (median, 2 months). Convulsion was the most common presenting
had glucagon injection 30 μg/kg as a therapeutic measure for hypoglycaemia and to confirm the diagnosis of hyperinsulinism. Ammonia level was measured in 14 patients and found to be elevated in one. MRI and CT studies showed that 14 patients had brain atrophy and neurological assessment showed that 18 babies had developmental delay. Twelve patients had a cardiac murmur, ventricular septal defect was detected in six and bicuspid valve in two.

Nine patients had successful medical management, while the remaining 34 underwent near total pancreatectomy because of failure of medical treatment. No patient was found to have a localized lesion (adenoma). All of them had open laparotomy except one who had a laparoscopic pancreatectomy. Postoperative complications included prolonged ileus in five patients and leakage in one, which stopped eventually. One patient had bile leak from an opening in the gallbladder. There were no injuries to the common bile duct. Two patients had recurrent intestinal obstruction requiring laparotomy. Four patients had a repeat pancreatectomy, three of which were performed shortly after the first (2–4 weeks) because of failure to control hypoglycaemia. The fourth case had a second operation 8 months after the first and was found to have overgrowth of the remaining pancreas. The child responded well to surgery. Side effects during medication included hypertrichosis in 20 patients, leukopenia in four, and thrombocytopenia in three. The duration of diazoxide treatment ranged from 1 week to 4 years (median, 15 months). Octreotide were first used in 1992 and 27 patients were treated with octreotide as an adjunctive therapy to diazoxide. The duration of octreotide treatment ranged from 1 week to 5 years (median, 18 months). One patient had the serious octreotide-related complication of bowel gangrene, which resulted in short gut syndrome with bowel length of 49 cm. He also had severe cardiomyopathy. Four patients died, two because of sepsis and two because of hypoglycaemic seizure. Six patients were lost to follow-up. Five patients were followed until the age of 1 year. Four of them were diabetic and two had malabsorption symptoms. One patient had prolonged diazoxide treatment for 10 years. Eighteen patients have significant developmental delay. Eight patients had intelligent test which ranged from 43 to 84 and four patients are blind and deaf. All except three patients have normal height velocity.

**Discussion**

Insulin is normally released by the β-cell of the pancreas, which is controlled by KATP channels and the entry of calcium, which is the specific stimulation of the exocytosis of insulin. There are two proteins known to be necessary for the balance of KATP channel and these two proteins are coded for by the sulfonylurea receptor (SUR1) gene and inward rectifying potassium channel subunit (Kir6.2) gene. It has been reported that anomaly of this gene is recognised in less than 60% of patients with PHHI, which explained inappropriate release of insulin by the β-cells. It has been reported that the incidence of PHHI is 1/50,000 live births; however, in areas with high consanguinity such as Saudi Arabia and Ashkenazi Jewish populations, the incidence could be as high as 1/2,500 live births. Most of the cases are sporadic but in our series, we have more than 67% with a family history as we have shown one family had seven affected siblings and four families have more than one child affected. Twenty of our patients had hypoglycaemic convulsion and developmental delay. High percentage of patients with varying degrees of brain atrophy might be the result of late referral and unresponsiveness to medical therapy. Although there is no documented correlation between the time of surgery and developmental delay, it is clear that the later the referral, the more is the brain damage. Hypoglycaemic convulsion was the commonest presenting symptom. The majority of our children had high insulin levels (36 mmol) and insulin to glucose ratio, which may indicate that they harbour the SUR1/Kir6.2 mutations. Patients with SUR1/Kir6.2 mutations are usually unresponsive to medical therapy and require surgery. These levels are higher than those reported in other studies.

Pancreatectomy in all patients in our series was performed by the open technique, except in one patient who...
underwent laparoscopic subtotal pancreatectomy (85%). During surgery, none of our patients were identified to have a focal lesion. Four of our patients underwent a repeat pancreatectomy because of failure to control hypo-glycaemia, which accounts for about 9% of cases. Despite this, we had four mortalities, none of which were related to surgical intervention. We observed a lower rate of other complications, particularly common bile duct injury, which is probably related to careful identification of the common bile duct. It has been reported that there is a higher incidence of repeat pancreatectomy in patients who undergo 90% resection,13 where in one series 18% of patients who underwent less than 90% resection required a further pancreatic resection.15 In another series of 165 children of 95% and 98% pancreatectomy, only 4.8% required further pancreatic resection.16 The extent of pancreatic resection in our patients ranged between 90% and 95% except in the laparoscopic case, which was about 85%. Further resection was required in four cases accounting for about 9% of pancreatectomy and we think our high rate of resection compared to other series is because all our cases were of a diffuse form. Pancreatic growth has been implicated as a possible cause of recurrence of hypoglycaemia and it was definitely observed in one of our babies, which was done during the neonatal period. He had significant residual and growth of the pancreas when resection was done 8 months later. This patient had responded very well to re-resection. Insulin dependent diabetes appears to be related to pancreatic resection13,17,18 and we have found that four out of five cases in our group above the age of 12 years have diabetes, and one of the medically treated groups. Pancreatic exocrine function of one patient (14 years) has also been affected by pancreatic resection, two of our patients had significant malabsorption that required pancreatic enzyme supplement, accounting for about 5%, and is comparable to literature reports,19,20 with some up to 10%.

Medical therapy with diazoxide and octreotide has been reported to be successful in some cases; however, 34 of our patients required pancreatectomy.

We conclude that PHHI is relatively common in Saudi Arabia, which is related to high consanguinity. Early medical intervention is extremely important to avoid neurological complications. We recommend prenatal counselling in families with affected children. Surgery is required in the majority of babies, but medical management can be successful in certain cases. We believe that the natural history of this disease is the development of diabetes mellitus, which can be accelerated by pancreatectomy. Care and spending more time to visualize the common bile duct help to avoid injury.

References


