Near-total pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy (nesidioblastosis): Mansoura experience
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Background/purpose Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of persistent hypoglycemia in infancy with consequences such as seizures and brain damage. Treatment that prevents the occurrence of these sequelae is essential.

When medical therapy fails or complications are anticipated, early pancreatectomy is recommended to maintain euglycemia. The aim of this study was short-term evaluation of near-total pancreatectomy for PHHI after failure of medical treatment in patients in Mansoura, Egypt.

Patients and methods During May 2002 to May 2010, 33 patients suffering from persistent hyperinsulinemic hypoglycemia were admitted to Mansoura University child hospital. Twenty patients responded to medical treatment and 13 patients (eight girls and five boys) were treated by near-total (90–95%) pancreatectomy after failure of medical treatment. Their ages at the time of surgery ranged from 20 days to 27 months. Only patients who were surgically managed were included in this study. All of them suffered from symptoms of PHHI: thermoregulatory problems in five cases, tremors in five cases, seizures in three, irritability in five, respiratory distress in eight, apnea in four, hypotonia in four, lethargy in five, and feeding difficulty in four cases. All cases were diagnosed following strict criteria that included bouts of hypoglycemia without acidosis coinciding with increased insulin level. Follow-up ranged from 3 months to 8 years.

Results Primary success occurred in two cases (15%); four more cases (31%) developed temporary diabetes mellitus, and one case (8%) had a temporary pancreatic fistula. Eventually, total cure occurred in seven cases (54%); six cases (46%) developed a variety of complications; and persistent hypoglycemia was seen in two. Persistent diabetes mellitus was observed in three patients, developmental delay in one, and persistent neurological deficit in two patients; there was one case of mortality.

Conclusion Near-total (90–95%) pancreatectomy is a suitable procedure for treatment of nesidioblastosis not responding to medical treatment and should be performed as early as possible. Ann Pediatr Surg 8:49–53 © 2012 Annals of Pediatric Surgery.

Introduction Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of recurrent and persistent hypoglycemia in infancy and childhood. Causes include PHHI, pancreatic islet cell tumors such as insulinoma, and associations with multiple endocrine neoplasia syndromes. Although new, improved imaging techniques have allowed for more precise preoperative localization of insulinomas, the differentiation of nesidioblastosis and insulinoma, particularly in children, can be challenging [1].

Congenital hyperinsulinism of infancy (CHI) is biochemically characterized by the dysregulated secretion of insulin from pancreatic β-cells. It is a major cause of persistent hyperinsulinemic hypoglycemia in newborns and infants. Histologically, there are three major subtypes of CHI: diffuse, focal, and atypical forms. The diffuse form is inherited in an autosomal recessive (or dominant) manner; the focal form is sporadic in inheritance. The diffuse form of the disease may require a near-total pancreatectomy, whereas the focal form requires limited pancreatectomy [2,3].

The focal form represented 40–70% of all cases in one of the largest series published [4,5]. The focal lesion is characterized by adenomatous islet cell hyperplasia due to somatic loss of the maternal chromosome 11p15 region within a limited region of the pancreas [6]. Endocrine hyperplasia and excessive β-cell proliferation within the focal lesion is due to loss of expression of maternally expressed tumor suppressor genes p57KIP2 and H19 and upregulation of the paternally expressed IGF-2 gene [7,8]. The adenomatous hyperplasia alone is not sufficient to cause hypoglycemia; the patient also has to carry a paternally inherited recessive SUR1 (ABCC8) or Kir6.2 (KCNJ11) mutation. Because of the maternal loss of heterozygosity, the mutation is able to cause dysregulated insulin secretion [9,10].

Distinction between the two histopathological forms is clinically important as near-total pancreatectomy carries a high risk of iatrogenic diabetes, whereas patients with focal CHI can be completely cured by a limited resection of the hyperfunctional tissue [11]. Until now, differential diagnosis before surgery has been difficult. Invasive and technically demanding techniques based on pancreatic...
venous sampling or pancreatic arterial calcium stimulation have been used [5,12]. Although found useful in many cases in some centers, these methods have not been widely accepted or implemented.

Diazoxide is the first line of treatment for patients with PHHI. Diazoxide and somatostatin (octreotide) are the mainstays of medical treatment for the condition. Also, successful therapy with nifedipine has been documented [13,14].

PHHI is treated surgically in many centers (near-total and partial pancreatectomy for diffuse and focal disease, respectively). Some of the patients treated with near-total pancreatectomy developed diabetes during childhood/puberty [15].

PHHI patients are at increased risk for neurodevelopmental disorders, some being severe, which were reported to occur in 14–44% of patients from highly heterogenous cohorts. A more conservative approach is now possible since the separation of the disease into a nonrecurring focal form, which is cured by partial surgery, and a diffuse form, which necessitates total pancreatic removal only in cases of medical treatment failure [16].

The aim of this study was to conduct a short-term evaluation of near-total pancreatectomy for PHHI in patients in Mansoura, Egypt, after failure of medical treatment.

**Patients and methods**

From May 2002 to May 2010, 33 patients suffering from persistent hyperinsulinemia hypoglycemia were admitted to Mansoura university child hospital. Twenty patients responded to medical treatment and 13 patients (eight girls and five boys) were treated by near-total (90–95%) pancreatectomy (Figs 1–4) after failure of medical treatment. Their ages at the time of surgery ranged from 20 days to 27 months (mean age 6.8 ± 7.2 months).

The following laboratory investigations were conducted:

1. complete blood profile,
2. liver function tests,
3. fasting blood glucose levels,
4. blood gases,
5. serum insulin levels in conjunction with blood glucose levels,
6. glucagon test.

Only patients who were surgically managed were included in this study, as our aim was to evaluate the efficiency of surgery in management of cases of PHHI after failure of medical treatment.

All patients suffered from symptoms of PHHI (Table 1) and were diagnosed following strict criteria that included bouts of hypoglycemia under fasting conditions without acidosis in association with increased insulin level as well as positive response to 1 mg glucagon subcutaneously (Table 2).

Medical treatment comprised somatostatin and nifedipine for 2 weeks, as diazoxide is not routinely used because of limited availability in Egypt.

**Fig. 1**

Dissection of pancreas reaching the head.

**Fig. 2**

Near total pancreatectomy completed showing the superior mesenteric and the splenic veins.

**Technique of surgery**

The procedure is accomplished by a generous upper transverse abdominal incision. Division of the gastrocolic omentum and the lowest short gastric vessels affords an excellent view of the whole pancreas. The uppermost
short gastric vessels are preserved if possible without compromising exposure. Following incision of the retroperitoneal investment of the gland along the inferior surface, and division of the splenic peritoneal reflections, complete mobilization and elevation of the spleen and pancreas is possible along the avascular retropancreatic plane. This facilitates careful bimanual palpation of the gland. A Kocher maneuver allows inspection of the pancreatic head. If no nodule is palpated, near-total pancreatectomy is undertaken. Dissection of the pancreas from the splenic vessels was performed, meticulously dividing all pancreatic branches using cautery and 6/0 silk ligatures, starting at the tail and moving all the way to the superior mesenteric vein and crossing it by dissecting the uncinate process and most of the head, leaving only a small remnant (~1 g) adjacent to the second part of the duodenum.

Excision of the tail, body, uncinate process, and most of the head of the pancreas was carried out ensuring that the common bile duct was not injured and ligating the pancreatic duct with nonabsorbable sutures.

Thus, 90–95% pancreatectomy was achieved.

All 13 pancreatic specimens were sent for postoperative histological examination. However, intraoperative histological analysis was not attempted.

Strict control of blood sugar level between 100 and 200 mg/dl was achieved at the time of surgery and for days thereafter using intravenous fluid and insulin early through infusion at a rate ranging from 0.05 to 0.1 IU/kg/h, then according to hourly blood sugar assessment through the subcutaneous route. Insulin treatment was needed only in those with early-onset diabetes mellitus. Follow-up ranged from 3 months to 8 years.

**Results**

Thirteen patients (eight girls and five boys) were treated by near-total pancreatectomy after failure of medical treatment.

Primary success occurred in two cases (15%); 4 cases (31%) developed temporary diabetes mellitus, and one case (8%) had a temporary pancreatic fistula. Eventually, total cure occurred in seven cases (54%).

The cases with primary success had no complications and were euglycemic directly postoperatively and stayed that way all through the follow-up. The patient who developed temporary diabetes and the patient who had temporary pancreatic fistula eventually recovered completely and were thus added to our number of successfully treated patients, increasing the total number of successfully cured patients to seven.

Six cases (46%) developed a variety of complications: hypoglycemia persisted in two cases, diabetes occurred in three cases, one case showed developmental delay, two cases showed persistent neurologic deficit, and one unfortunately died (Table 3).
The earliest two patients showed persistent hypoglycemia, which was controlled by medical treatment.

The three patients who developed diabetes were also considered to be successful, as they were cured of PHHI. One developed diabetes 10 days after surgery, whereas the other two developed diabetes 2 or 3 months after surgery, which was controlled by low-dose insulin. This raised the success of the procedure to 10 cases (77%). One patient died of sepsis that was unrelated to the procedure.

To our dismay, all histological specimens were inconclusive and could not differentiate focal from diffuse lesions.

**Discussion**

PHHI is the most common cause of refractory hypoglycemia during the first year of life. It is a rare condition presenting with severe hypoglycemia. Prompt diagnosis and early pancreatectomy can save many children, despite the magnitude of surgery [17,18].

Timo Otonkoski and colleagues studied 14 patients with PHHI and found that it is possible to identify the focal forms of CHI using noninvasive fluorine-18-l-dihydroxyphenylalanine (18F-DOPA) PET. They found focal accumulation of 18F-DOPA in the pancreas of five patients, and a focal lesion was confirmed histologically in each case. All these infants underwent limited pancreatic resection guided by perioperative biopsies, and all of them have remained normoglycemic without treatment. Diffuse pathology was confirmed in four of the nine patients showing diffuse pancreatic accumulation of 18F-DOPA and were treated by near-total pancreatic resection [19].

We did not have the luxury of using invasive and technically demanding techniques based on pancreatic venous sampling or pancreatic arterial calcium stimulation or 18F-DOPA PET in our study. This was because of the nonavailability of these techniques in our establishment, which made it impossible for us to preoperatively differentiate focal from diffuse forms. All our postoperative specimens were sent for histological examination but were not conclusive because of lack of experience among our pathologists.

The study by Al-Nassar and colleagues, a long-term retrospective study in which 43 Saudi children with PHHI, has been followed up since 1983. The patients were severely hypoglycemic and intolerant to fasting. Hypoglycemic 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 [20].

In our series 13 of 33 patients were managed surgically, which is a larger number than that in the study by Al-Nassar and colleagues, and we also showed a lower incidence of complications. This in our opinion is related to our early decision to operate upon patients who did not respond to medical treatment.

Meissner and colleagues conducted a large long-term cohort study on 114 CHI patients from different hospitals, the results of which were obtained using a detailed questionnaire. Patients presented neonatally (65%), during infancy (28%), or during childhood (7%). They observed a high rate of pancreatic surgery in the neonatal-onset group (70%) compared with the infancy/childhood-onset group (28%). Partial (3%), subtotal (37%), or near-total (15%) pancreatectomy was performed. After pancreatic surgery there appeared a high risk of persistent hypoglycemia (40%). Immediately after surgery or with a latency of several years insulin-dependent diabetes mellitus was observed in patients operated upon (27%). General outcome was poor with a high degree of psychomotor or mental retardation (44%) or epilepsy (25%). An unfavorable outcome was correlated with infancy-onset manifestation (P = 0.01) [21].

We believe that near-total pancreatectomy gives optimal results for control of PHHI and that the results of Meissner and colleagues would have been much better if they had used this procedure in all patients.

Further, Lovvorn and colleagues found in his retrospective study on 101 children treated between 1963 and 1998 for congenital hyperinsulinism, and who required pancreatectomy, that subtotal (< 95%) or near-total (95–98%) pancreatectomy had been performed for glycemic control in babies who did not respond to aggressive medical therapy. They recommended that because euglycemia is more readily restored, and because the risks for surgical complications and diabetes mellitus do not appear increased, 95% pancreatectomy be the initial procedure of choice for newborns and infants with congenital hyperinsulinism [22].

The results of the above study were found to be in total agreement with those of our series.

Al-Shanafey and colleagues managed 12 patients diagnosed with PHHI by laparoscopic 90% pancreatectomy. There were two (16%) conversions to an open technique. One patient required reoperation 3 months after the procedure. Four (33%) were euglycemic with no medications. Three patients remained on octreotide postoperatively to be euglycemic, and three patients needed a combination of octreotide and diazoxide. One patient remained euglycemic for 10 months and was then started on octreotide because of recurrence of hypoglycemia. One patient remained hypoglycemic postoperatively and required reoperation 3 months later to control symptoms.
He became diabetic 4 months after reoperation and was prescribed insulin. These data proved that laparoscopic pancreatectomy was feasible and safe [23].

In our study, we did not attempt laparoscopic pancreatectomy but we also believe that it is feasible and safe in experienced hands, however expensive.

We hope that in the future we would be able to apply advanced investigations and accurate histological examination as we try to make them available at our facility. We believe that these would lead to better and more accurate management of patients with PHHI.

Conclusion
Near-total (90–95%) pancreatectomy is a suitable procedure for treatment of patients with nesidioblastosis not responding to medical treatment and should be performed as early as possible.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

References