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PANCREATIC FUNCTIONS AND DEVELOPMENTAL OUTCOME AFTER SURGICAL MANAGEMENT OF PERSISTENT NEONATAL HYPERINSULINEMIC HYPOGLYCEMIA

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We evaluated the detailed pancreatic endocrine and exocrine function in children with persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) 95% pancreatectomy. Seven children with PHHI between 0.9 and 5.2 years after pancreatic resection underwent clinical and investigative follow up. Three children with PHHI who had not had pancreatectomy were also assessed. Standard endocrine assessment, pancreatic magnetic resonance imaging (MRI), and detailed direct and indirect tests of exocrine pancreatic function were performed. Pancreozymin-secretin stimulation test results were deficient in four out of the seven patients, one of whom had frank steatorrhea required daily pancreatic enzyme supplements.

One child developed insulin dependent diabetes at 3 years and two children had impaired glucose tolerance. MRI showed no major re-growth of the pancreatic remnant after resection (n = 4). The height SD score, growth velocity SD score and BMI were significantly lower in Children who underwent near-total pancreatectomy vs. non-pancreactomised children. The head circumference was markedly smaller in the non-pancreactomised children and all of them had poor neuro-developmental outcome, with global developmental delay and neurological abnormalities. Two out of the seven pancreactomised children had developmental delay and spastic cerebral palsy. Circulating IGF-I and basal GH concentrations were lower in the pancreactomised group. Their basal and glucagon-stimulated C-peptide concentrations were significantly decreased compared to the non-pancreactomised children. Basal growth hormone (GH) levels were higher in the non-pancreatectomized group.

Growth hormone response to provocation was adequate in both groups. HbA1C concentration was significantly lower in the non-pancreactomised group as well as their fasting and 2h-post prandial blood glucose levels compared to pancreactomised children. Clinical evidence of endocrine dysfunction has developed in three patients (1 with IDDM, and 2 with IGT). Three patients had subclinical deficiency of one or two exocrine pancreatic enzymes but only one had multiple enzyme deficiencies and steatorrhea and required pancreatic enzyme replacement. Although 95% pancreatectomy results in postoperative control of blood glucose, the development of IDDM, impaired linear growth, and exocrine failure remain ongoing risks.

Key words: Neonatal hypoglycemia, Hyperinsulinemia, Pancreatectomy, Nesidioblastosis, Exocrine, Endocrine, Growth, Development and Hormones

INTRODUCTION

Persistent hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) is a diagnosis of importance as hypoglycemia may be exceedingly difficult to control, and associated with it is a high incidence of brain damage and subsequent mental retardation. [1, 2] In 1938, Laidlaw coined the term nesidioblastosis to describe the differentiation of islets of Langerhans from pancreatic ductal epithelium. In nesidioblastosis there is a continued uncontrolled proliferation of pancreatic ductular endocrine cells replacing the normal islets and infiltrating the acinar tissue. [3] Unlike the gradual and controlled increase of insulin release from the normal islet cells [3-5] insulin secretion from

isolated nesidioblastosis cells is effectively autonomous. [2] The hormone (insulin) is released at a high rate even in the absence of secretagogues e.g. glucose. [6] Severe, recurrent hypoglycemia associated with this inappropriate elevation of circulating insulin, C-peptide, and proinsulin concentrations characterizes this disorder. [1,2,13]

This functional/structural abnormalities in the insulin secretory mechanism or glucose sensing mechanism result in a failure to reduce pancreatic insulin secretion in the presence of hypoglycemia (serum glucose <60 mg/dL). Inappropriately high circulating insulin levels act to promote hepatic and skeletal muscle glycogenesis causing a decrease in the amount of free glucose available in the bloodstream and suppression of the formation of free fatty acids (FFA), an alternate energy substrate for the brain. The net effect is severe and dangerous hypoglycemia, which results in physiologically appropriate adrenergic and neuroglycopenic symptoms with severe neurologic dysfunction and frank seizure activity when CNS glucose levels fall below 20-30 mg/dL. [4,6,7]

Infants with nesidioblastosis have excessive insulin secretion in utero, but in contrast to infants of diabetic mothers, this secretion is sustained after neonatal period. [7-10] Prolonged hypoglycemia might cause death. Repeated episodes of severe, prolonged sublethal hypoglycemia can result in permanent neurologic damage including developmental delay, mental retardation, cerebral palsy and/or focal CNS deficits. Therapy should be aimed at prevention of hypoglycemia to prevent morbidity and mortality.

The mainstay of medical treatment includes increasing carbohydrate intake with frequent high calorie enteral feeds or intravenous glucose at a rate above 15 mg/kg/minute diazoxide1-3 and octreotide.4 these measures usually fail, and surgical resection of the pancreas is considered the best choice of treatment up till now. The degree of pancreatic resection should be such that hyperinsulinism is abolished or is controllable by medical treatments, but not so excessive as to render the patient's exocrine and endocrine function insufficient in the long term.[19,22]

The term nesidioblastosis has been replaced by several synonyms, including persistent hyperinsulinemic hypoglycemia of infancy (PHHI), which is the most commonly used term. Two broad subtypes of PHHI have been well described. These include a focal adenomatous hyperplasia type and diffuse types.

Focal adenomatous hyperplasia is found in one fourth to one third of cases and the diffuse abnormality of the islets occurs in the rest of the cases.[10,11,20]

The genetic defect responsible for the disease has been mapped to chromosome 11p14-15.1 by linkage analysis in 15 families. [10]. Recent advances in elucidating the molecular basis of this condition have led to the discovery of an array of mutations in the ATP-sensitive potassium channel (a functional complex of the sulfonylurea receptor 1 [SUR1] and an inward rectifier potassium channel subunit [Kir6.2] that regulates insulin secretion). The glucokinase gene (GK) and the glutamate dehydrogenase gene (GLUD1) also have been implicated. Other candidate genes have been proposed, but have not been identified yet.[4,16]

Nesidioblastosis often is poorly responsive or unresponsive to medical management such as diazoxide, depot-glucagon, somatostatin and other anti-insulin medications. This necessitates pancreatectomy in the majority of cases. The extent of resection continues to be controversial. The original subtotal pancreatectomy (65%) resection was attended by a 50% recurrence rate. Less than 80% resection resulted in 45% recurrence and 26% needed reoperation for persistent hypoglycemia. Figure 2 shows the amount of pancreatic resection in each type of pancreatectomy. In comparison 28% of patients undergoing subtotal pancreatectomy required a second operation compared with 5% of patients with 95-98% near-total pancreatectomy. A 95% resection is claimed to produce the best overall results. The reduction of hormone producing tissue resolves hyperinsulinemic hypoglycemia.[15]

Aim of the work:

This study aimed to investigate pancreatic exocrine and endocrine function and evaluate growth and developmental achievement of our patients with PHHI after near-total pancreatic resection. Three additional children who were managed solely by medical treatment were also investigated.

PATIENTS AND METHODS

All infants and children referred to Alexandria University Children's Hospital during the past 5 years for medical and/or surgical management of PHHI were included. In total there were 10 children: seven were operated upon using the near-total resection (95% pancreatectomy). Two patients presented late after occurrence of cerebral palsy , they were suffering from spastic quadriplegia and grandmal seizure, and they died after 7 and 11 months after surgery. None died in the immediate postoperative period. All parents gave consent for investigation. Three children (Cases 8, 9, 10) were managed medically without recourse to surgery. Median gestational age was 39.5 weeks (range 35-41), and median birth weight 4600 g (range 2230-5200), which placed eight of the ten children above the 97th centile for weight at birth. There were three girls and seven boys. Median age at

pancreatic resection was 91 days (range 26 days to 6 months). Median age at the time of the pancreatic function study was 1.25 years (range 1.0- 5.2) (Table 1).

Patients were admitted to the ward on the morning of investigation having had a light breakfast. The one child on pancreatic enzyme supplements had stopped taking them one week before admission. Intravenous access was obtained and blood taken for clotting studies, fat-soluble vitamin concentrations, serum immunoreactive trypsin, haemoglobin A1c, and islet cell antibodies.

Patients were admitted to the day case unit on the morning of investigation having had a light breakfast. The one child on pancreatic enzyme supplements had stopped taking them one week before admission. Intravenous access was obtained and blood taken for clotting studies, fat soluble vitamin concentrations, serum immunoreactive trypsin, haemoglobin A1c, and islet cell antibodies.

Pancreozymin-Secretin Test

After oral sedation with chloral hydrate and midazolam, a Merck Corflo silk enteral nasoduodenal feeding tube was passed under fluoroscopic guidance so that the tip of the tube was at least beyond the second part of the duodenum. Duodenal juice was then collected continuously for a period of 50 minutes, batched in 10 minute aliquots, and frozen immediately in liquid nitrogen. Two Ivy Dog Units/kg body weight of pancreozymin and 2 IU/kg of secretin were given intravenously at 0 and 20 minutes, respectively. Pancreatic enzyme activity was calculated/kg body weight/50 minute test according to the method by Hadorn.13 Chymotrypsin, lipase, and pancreatic amylase were assayed by kinetic methods using commercially available kits (Boehringer Mannheim UK, Lewes, East Sussex, UK).

Pancreatic Imaging

An ultrasound scan of the pancreas was also done for all the patients. Three patients underwent magnetic resonance imaging (MRI) using a 1.5 Tesla Philips gyroscan NT system with T1 and T2 weighted images.

Glucose Tolerance Test

The glucose tolerance test was done on patients not requiring diazoxide or insulin. Blood for serum glucose measurement was taken at 0 minutes. A glucose load of 1.75 g/kg was given enterally and the serum glucose checked at 120 minutes.

Faecal Chymotrypsin

Stool was collected on three consecutive days from all but one child and an average of the three values taken.14 Analysis was done by kinetic methods using a Boehringer Mannheim kit (product number 718211).

Ethics

The study was approved by the ethics committee of Alexandria University Ethics Committee. Parents received full written information sheets on the nature of the study and fully informed written consent was obtained.

RESULTS

Of the 10 children who have had PHHI over the past 5 years, 7 were managed surgically, with two deaths 7 months and 11 months after surgery because of severe aspiration pneumonia with cerebral palsy and severe mental retardation. A 95% pancreatectomy was undertaken in all the 7 infants. No child required a further pancreatic resection because of postoperative hypoglycaemia. The other 5 living children were available for detailed study of pancreatic function together with 3 additional children who had not undergone surgery (Table 1). Of these seven pancreatectomized children (Table 2), one continues to require diazoxide to prevent hypoglycaemia; nearly 18 months after a 95% pancreatectomy (patient 5). One child has developed insulin dependent diabetes requiring Mixtard 30/70, 6units in the morning and 4 units in the evening (weight 22 kg). One child still requires starchy supplementary feeds every 3-4 hours to maintain blood glucose concentrations. One child takes 1 capsule of Creon (pancreatin; Duphar, Southampton, UK) with meals because of steatorrhoea. Two children have severe developmental delay, (patients 2, 7) and one of them had grandmal seizure attacks (patient 2) and receives carbamazipine. Both were operated later than 5 months after birth with several attacks of intractable hypoglycemia and fits in their early neonatal period with delay in the diagnosis and referral to our center.

Out of the 3 children who did not undergo pancreatic resection, because parents refused to give consent for the operation, 2 died during severe and intractable attacks of hypoglycemia at the age of 7 and 11 months. The survivor (patient 8) is still on dietary supplements and diazoxide +/- nefidipine. He still has attacks of significant hypoglycemia and he suffers from moderate to severe developmental delay, microcephaly and cerebral palsy (spastic type). He has grandmal epilepsy and receives carbamazipine (Table 2)

Pancreozymin-secretin stimulation tests (Table 3) showed decreased amylase and lipase activity in one child (patient 4); decreased chemotrypsin activity in three (patients 1, 3, 4); decreased amylase in three (patients 2, 3, 4); and decreased lipase in three (patients 1, 3, 4). One patient (4) had combined deficiencies of the three enzymes

Faecal chymotrypsin was below the normal reference

range in only one child (patient 4). This was in agreement with his very abnormal pancreozymin secretin test. Fat soluble vitamin concentrations were generally within the lower limit of the normal compared to the reference range. One child had subnormal vitamin A concentrations (Table 4). Clotting studies were all normal reflecting normal vitamin K action.

Two of the children (patients 1, 2) had impaired glucose tolerance tests done according to WHO criteria. Fasting and 120 minute serum glucose values (mmol/l) after a standard 1.75 g/kg body weight glucose load were 4.3, 4.8 and 7.5 and 7.7 respectively. One patient (6) had IDDM.

(Table 5) represents some clinical and hormonal data of pancreactomised versus non-pancreactomised children. The height SD score, growth velocity SD score and BMI were significantly lower vs. non-pancreactomised children. The head circumference was markedly smaller in the non-pancreactomised children. Circulating IGF-I and basal GH concentrations were lower in the pancreactomised group. Their basal and glucagons- stimulated C-peptide concentrations were significantly decreased compared to the non-pancreactomised children. Growth hormone response to provocation was adequate in both groups. HbA1C concentration was significantly lower in the non-pancreactomised group as well as their fasting and 2h-post prandial blood glucose levels compared to pancreactomised children.

MRI and ultrasound imaging of the pancreas visualized only small remnants of pancreatic tissue in the region of the head of the pancreas around the common bile duct consistent with our 95% pancreatectomy (Fig. 1). Although immediate postoperative scans were not available for comparison, significant pancreatic regeneration could not be shown in any of the children. Ultrasonography of the pancreatic remnant yielded less detailed images of the pancreatic remnant than MRI.

Pathologically no focal lesions could be seen in any of the 7 cases .The pancreas was diffusely affected but not enlarged. Removal of about 95% of the pancreas was done by removing the tail, body, the uncinate process and most of the head except for a thin rim near the duodenum and CBD. Surgical complications included incidental perforation of the duodenum during dissection with diathermy in case no.3 region of the head which was repaired with interrupted absorbable sutures and healed uneventfully.

Postoperatively 4 of the 7 patients had mild form of hypoglycemia which was managed with frequent feeds containing starch. Prepandial hypoglycemia and postprandial hyperglycemia occurred in 3 patients for 2-4 weeks which denoted disturbed fine tuning of glucose homeostasis.

Table 1: ***Birth weight, gestation period and extent and age of pancreatectomy***

Patient	B. Wt (g)	Gestation (w)	Age at oper	Pancreatec. (%)
1	3700	40	0.1	90
2	5200	41	0.5	90
3	2230	36	0.4	95
4	3400	41	0.1	95
5	4800	39	0.1	95
6	4600	41	0.3	90
7	4600	41	0.6	95

Gestation = gestation age, Age of oper = age at operation in years
% = % of pancreatic tissue removed .

Table 2: ***Clinical outcome of patient***

Pts	*Glycemia*	*Enzyme supplement*	*Current drugs*	*MR*	*CP*
1	IGT	No	Nil	No	No
2	IGT	No	Carbamazepine	Yes	Yes
3	Normal	Yes	Nil	No	No
4	Normal	No	Pancreatin	No	No
5	Normal	No	Food suppl	No	No
6	IDDM	No	Insulin	No	Mild
7	Normal	No	Diazoxide	Yes	Yes
8	Hypogly	No	Diazoxide + CS	Yes	Yes
9	Hypogly	No	Diazoxide + nefidepine	Yes	Yes
10	Hypogly	No	Diazoxide	Yes	Yes

IGT = impaired glucose tolerance, IDDM = insulin-dependent diabetes mellitus
Hypogly = hypoglycemic
*=DIED

Table (3): *Pancreozymin-secretin test results in pancrectomized patients*

Pt	*Volume (ml/ kg)*		*Amylase (IU/kg)*	*Lipase (IU/kg)*
1	*1.3*	135	87.5	126
2	ND	ND	ND	ND
3	1.1	142	25.7	112
4	0.4	121	15	*26*
5	ND	ND	ND	ND
6	0.2	280	125	*230*
7	1.3	577	187.8	*221.2*
Mean	0.86	251	88.2	143
Reference range	1.2-7.5	350-2700	90-1050	300-5000

IU/kg/bw/test/ B.W. = body weight.
ND: not done

Table (4): *Blood and stool results*

Patient- number	1	2	3	4	5	6	7
HbA1c (4.5- 6.5%)*	6.5	ND	5.7	5.4	ND	8.2	4.2
Islet cell antibodies	-ve	ND	-ve	-ve	ND	-ve	-ve
PT (s)	15/14	ND	18/ 16	14/ 13	ND	18/ 16	16/ 13
APTT (s)	33/36	ND	29/35	30/33	ND	28/36	30/33
Vitamin A (3-	3.3	ND	2.1	3.8	ND	2.9	4.7
Vitamin D (3-30 ng/ml)*	23.2	ND	25.3	13.5	ND	22.5	25.0
Vitamin E (0.52- 12.2mg/100ml)*	1.14	ND	1.48	0.73	ND	1.23	0.69
Faecal chymotrypsin (>	67.6	ND	19.8	9.6	ND	19.2	147.4

-ve = negative,
*Reference normal values
ND=not done

Table (5): *Hormonal and Anthropometric Data of Pancreactomised Versus Non-pancreactomised Children with PHIH.*

	Pancreatectomised $n = 5$	*Non-pancreatectomised* $n = 3$
Age (years)	3.2 +/- 0.8	2.8 +/- 1
Ht	-2.2 +/- 0.25*	0.5 +/- 0.3
GV	-1.6 +/- 0.4	0.8 +/- 0.2*
BMI (kg/m2)	14.88 +/- 0.55	17.5 +/- 0.8*
Head circumference (cm)	48 +/- 0.8	46.2 +/- 1*
Free thyroxine (pmol/l)	15.5 +/- 2.3	14.2 +/- 2.1
TSH (mIU/l)	1.1 +/- 0.3	1.3 +/- 0.3
Growth hormone (ug/l)		
Basal	1.65 +/- 1.2	5.2 +/- 3.5*
Peak after clonidine	12.5 +/- 2.5	15.6 +/- 2.2*
IGF-I (ng/ml)	82 +/- 35	179 +/- 50*
C-peptide (ng/ml)		
Fasting	0.75 +/- 0.26	4.8 +/- 1*
6-min after IV glucagon	1.1 +/- 0.5	7.9 +/- 1.38*
Hb A1C (normal : 4.2 : 6.5%)	7.1 +/- 1.5*	3.7 +/- 0.2
Glucose (mmol/l)		
Fasting	6.3 +/- 1.5*	3.2 +/- 0.7
2 h-after oral glucose (1.75 g/kg)	7.9 +/- 1.3*	4.5 +/- 0.5

- $p < 0.05$ pancreactomised versus non-pancreactomised
- Glucagon test (0.1 mg/kg , max. 1 mg, given i.v and glucose measured before and after 6 minutes)
- Ht: height
- GV: growth velocity

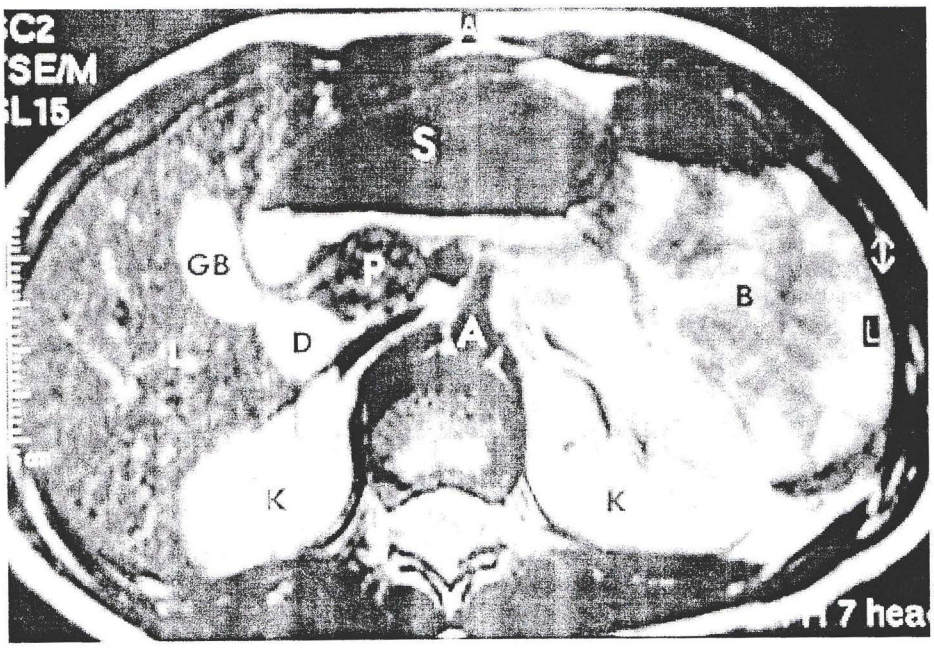

Fig. (1): MRI showing the remnant of the pancreatic head (T2 weighted image at the level of the renal hila) 2 months after surgery in patient 7.

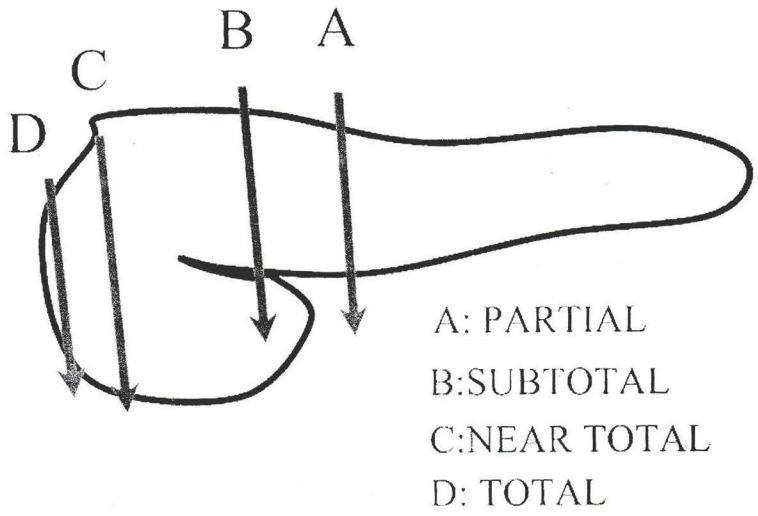

Fig. (2): The different types of pancreatectomy

DISCUSSION

Early diagnosis of PHHI in any infant with refractory hypoglycaemia, and immediate and appropriate treatment is imperative to prevent hypoglycaemic injury to the neonatal brain. In this study and others, infants with PHHI who presented after the first few weeks of life had the worst prognosis, with significant degrees of mental retardation, microcephaly and cerebral palsy.[2,6] Medical treatment, as the sole mode of management was associated with extremely high incidence of neurological damage and global developmental delay. Therefore, a majority of children requires surgical resection of the pancreas to control the hyperinsulinaemia.[15]

Many studies have addressed the controversy about the extent of pancreatectomy. In our series, mortality rate was lower in patients with pancreatectomy (2/7) versus without pancreatectomy (2/3). Neurological abnormalities and/or mental retardation occurred in 3/7 of the pancreatectomized infants. In our series, none of the pancreactomised patients (95% pancreatectomy) required further pancreatic resection for correction of hypoglycemia. In another study 18% of patients undergoing < 90% pancreatic resection required further pancreatic resection. In agreement, one big review showed an overall mortality rate of 10% (related to surgery) and an incidence of 54% mental retardation in survivors.

Another study on neonates who underwent 95-98% pancreatectomy reported an overall mental retardation rate of 12.5% with only 4.8% required a further pancreatic resection. This compared with a 28% reoperation rate in the same study for those having less than a 95% pancreatectomy. Since 1987 there have been several other studies concerning the extent of pancreatic resection and addressing the long term follow up of these patients. In all treatment groups, mental retardation and neurological impairment continue to be a significant complication of this condition with an overall incidence of 15%. Our rate of 37% is unduly high but may simply reflect our small sample size and/or delayed diagnosis and referral of these infants before the occurrence of significant brain damage.[6]

From this and other studies, with the high rate of unpreventable neurological damage and high mortality in non-operated infants, the so-called 95% pancreatectomy is generally accepted as the surgical treatment of choice. However, the diagnosis and surgical intervention should be made as early as possible to minimize the neurological complications of hypoglycemia.

Postmortem examinations of the pancreas, especially when the naked-eye appearance can not detect any

significant pancreatic enlargement or focal lesions, indicate that in practice the 95% resection in which only a small remnant of pancreas is left between the common bile duct and the duodenum appears to be the resection of choice and is less prone to anatomical variability

Pancreatic re-growth has been implicated as a possible cause for postoperative hypoglycemia in children with PHHI undergoing pancreatic resection. We were unable to show any evidence of significant pancreatic regrowth after pancreatic resection in any of our children using ultrasound and MRI imaging, although residual pancreatic head tissue was clearly shown. Pancreatic re-growth may therefore be a compensatory response to surgical resection and may represent only a temporary phenomenon that disappears over time.

The incidence of insulin dependent diabetes (IDDM) and impaired glucose tolerance was 43% (3/7) of our patients followed up for a mean of 3.5 years. This disturbed glucose homeostasis appears to relate not only to the extent of primary pancreatic resection but also to length of follow up. Leibowitz et al found that all six children reaching puberty who had undergone "subtotal" pancreatectomy for neonatal PHHI developed diabetes mellitus. Shilyansky et al showed a 69% incidence of diabetes mellitus in children with PHHI followed up for more than four years. Patient 6 in our study developed insulin dependent diabetes mellitus at 3 years of age.

Studying pancreatic exocrine function generally revealed defective individual enzymatic secretion in a good number of patients (3/7) (43%) but multiple enzymatic deficiencies with steatorrhoea occurred only in one patient who required pancreatic enzyme supplementation. Overall, only 1 child (14%) ware taking pancreatic enzyme supplements after 95% resection. Those children with subclinical exocrine insufficiency in response to pancreozymin - secretin stimulation are at risk to develop ultimately exocrine failure. Whether the extent of the pancreatic resection or simply the age of the child is the dominant factor in ultimate exocrine failure is unknown, because all the children were subjected to the same amount of resection and they are still young. However, exocrine function and stool fat content should be evaluated regularly in these patients, especially when accompanied with symptoms and signs of malabsorption or impaired growth.

Linear growth and BMI of non-pancreactomised patients were significantly better compared to pancreactomised children. This could be explained by their high circulating concentrations of basal IGF-I, insulin and GH vs. non-pancreactomised patients. In addition, high dietary carbohydrate associated with hyperinsulinaemia explains their high BMI. Impaired/defective insulin secretion and subclinical pancreatic exocrine deficiency can explain the relatively low BMI in pancreactomised children. Although the anthropometric data of non-pancreactomised children proved good linear growth and weight gain, their developmental and neurological outcome was disappointing.

In vitro studies indicate that calcium channel blockers may be able to reversibly block insulin secretion from the cells of patients with PHHI, 32 and this may allow the development of new therapeutic strategies in this disabling condition. In our experience, nefidipine therapy was initiated early in one non-pancreactomised patient (pt 9), in addition to frequent feeds, with significant improvement of hypoglycemia. However, this drug did not abolish hypoglycemic attacks and the patient suffered from mild global developmental delay. [3,14]

In 1994 a "PHHI gene" was localized to chromosome and later that same year mutations in the sulphonylurea receptor (SUR) gene were implicated. The SUR, a subunit of the cell membrane's ATP dependent potassium channel, is involved in regulation of insulin secretion. Gene mutations leading to a defective SUR protein may disrupt the activity of the potassium channel causing excessive insulin secretion. If it was possible to modulate activity of the SUR medically it may offer an alternative to surgical intervention. Not only would this abolish the need for complex pancreatic surgery but it may also postpone or prevent the progression to end stage cell failure. However, the transgenic mouse model of hyperinsulinaemia suggests that cell maturation and premature death may be inevitable in PHHI. The aetiology of PHHI has still not been fully determined and more than one cause is possible. It is important to be aware of the possible development of pancreatic (endocrine and exocrine) failure in children with PHHI and investigate these pancreatic functions regularly.[4]

In summary, in children who undergo 95% pancreatectomy (near-total pancreatectomy) for PHHI, the re-growth of the B-cell mass, and possibly the enzyme secreting acinar cells, appears to be compromised for maintaining long-term glucose tolerance and adequate linear growth. However, the neuro-developmental outcome appeared to be satisfactory in those patients who underwent the surgery early before significant hypoglycemic brain insult.

Immediate treatment of hypoglycemia is essential. Patients may require continuous IV glucose infusion. Glucagon also may be given acutely to maintain adequate blood glucose levels.

Patients should use a home glucose meter to monitor glucose levels. A physician should review the results periodically to assist in adjusting medications. More frequent glucose monitoring may be necessary during

illness, when changing medications, or after dose adjustments. During illness, when oral intake is lower, patients may be at higher risk for hypoglycemia. Patients with persistent vomiting or diarrhea may require hospital admission for IV glucose administration until they are able to tolerate oral intake. Continuous feeding by nasogastric or gastrostomy tube may be helpful in some patients to maintain adequate blood glucose levels. Continuous feeding particularly is useful during sleep. Diazoxide, octreotide, and nifedipine are the primary medications used in long-term treatment of nesidioblastosis. All are used widely for other indications and all (except nifedipine) are associated with increased serum glucose as a well-known adverse effect. The hyperglycemic action is beneficial in the treatment of nesidioblastosis, but their other therapeutic actions may become a burden in the patient with nesidioblastosis, who lacks the condition the drug was originally intended to treat. For example, diazoxide, primarily used as an antihypertensive, may cause hypotension in the normotensive child with nesidioblastosis. In addition, most agents have significant adverse effects, especially with long-term use. Nifedipine is a relative newcomer to the therapeutic armamentarium, and it appears to have considerably fewer adverse effects than the other agents.[14,21,22]

Varying doses for each drug have been used in different centers. The exact medication regimen, including doses and selection Of drugs, must be highly individualized based on therapeutic response, adverse effect tolerance, and individual factors (eg, patient acceptance of SC injections). Many patients will require years of drug therapy, and regular reassessment and dose adjustments will be required. Given the potential for significant adverse effects with chronic administration, patient adherence to the medication regimen may be suboptimal. The best way to assure good adherence is with open discussion of risks and benefits, regular follow-up, and individual tailoring of drug regimens.

If no focal lesion is found, the surgeon proceeds to perform a partial pancreatectomy. Extensive experience with varying degrees of pancreatic resection in infants and children has been reported. Although some controversy remains, the 95% or subtotal pancreatectomy is the most widely accepted procedure for infants and children. In this procedure, the tail, body, uncinate process, and majority of the head of the pancreas are removed, leaving a portion of pancreas to the right of the common bile duct and a thin rim along the second portion of the duodenum and the pancreaticoduodenal arteries. Resection of less than 95% of the pancreas is associated with a higher rate of treatment failure and need for reoperation. The 98% pancreatectomy removes all but a few small islands of pancreatic tissue along the pancreatico-duodenal arteries. This procedure is associated with a higher rate of diabetes mellitus postoperatively; however, patients with lesser degrees of pancreatic resection also remain at substantial risk for future development of diabetes mellitus. Future advances in medical therapy may provide better glycemic control with fewer side effects, permitting less radical pancreatic resection.[5]

Regardless of the procedure used, hypoglycemia may recur, and the patient may require continued medical therapy. Reoperation with additional pancreatic resection may be indicated if optimal medical management cannot provide adequate glycemic control. In rare refractory cases, total resection of the pancreas has been performed.

In infants, surgery usually is performed within the first 2 months of life.

Published material on the surgical management of adult nesidioblastosis is limited. The optimal extent of pancreatic resection necessary for optimal outcomes in adults is not known. Pancreatic resections ranging from 30-95% have been reported with widely variable results. Until more data are available, some authors have suggested a more conservative resection of the pancreas as the initial procedure in adults, with possible reoperation if adequate glycemic control is not obtained.[8,9,12]

Some authors have advocated cryopreservation of islet cells from the resected portion of the pancreas for possible future autotransplantation if the patient develops diabetes mellitus. This technique has been employed in limited numbers of adults undergoing total pancreatectomy for severe pancreatitis. The results have been variable, and the number of reported cases is small. Some patients with nesidioblastosis (or their families) have elected to have cryopreservation performed, but no cases of subsequent autotransplantation have been reported. The ethical, technical, and safety considerations related to this concept have not been developed completely. Patients or their families may wish to consider islet cell preservation in anticipation of possible future developments in this area.[17]

Prognosis:

Hypoglycemia often persists even after 95-98% pancreatectomy. Hypoglycemia may be easier to control after partial pancreatectomy, and may resolve months or years later or persist throughout life.

In one study of 101 patients, 50% of patients who underwent 95% or greater pancreatectomy were cured, that is, they did not require medical or dietary treatment to maintain normoglycemia within the follow-up time period of the study. The mean time from surgery to cure was 4.7 years.

Future development of diabetes mellitus

Patients who undergo partial pancreatectomy are at high risk for developing diabetes mellitus later in life. The risk of diabetes mellitus appears to increase with the extent of pancreatic resection; however, the risk is significant even with conservative surgical procedures.[5]

In one series, 14% of children with diffuse lesions developed diabetes mellitus, regardless of the surgical procedure performed. The mean time from surgery to development of diabetes mellitus was 9.6 years. Most series are limited by relatively short follow-up times, so the lifetime incidence of diabetes mellitus is not well understood.

In some series, a high frequency of mental retardation, developmental delay, and nonhypoglycemic seizures has been observed. These findings generally are attributed to minimal brain damage from early hypoglycemic events, although the existence of these disorders as inherent comorbid conditions with nesidioblastosis has not been fully excluded. Other series, usually in conjunction with medication studies, have shown normal developmental progress in patients with nesidioblastosis. No comprehensive, long- term studies of neurodevelopmental outcomes in patients with nesidioblastosis exist. It is unknown whether more aggressive treatment performed earlier, with a wider range of therapeutic options, will reduce these complications.

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