Pancreatic exocrine and endocrine function after pancreatectomy for persistent hyperinsulinaemic hypoglycaemia of infancy

A Cade, M Walters, J W L Puntis, R J Arthur, M D Stringer

Abstract

Aim—To evaluate long term detailed pancreatic endocrine and exocrine function in children with persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) after 85–95% pancreatectomy.

Methods—Six children with PHHI between 0.9 and 12.7 years after pancreatic resection underwent clinical and investigative follow up at 1.0 to 14.9 years of age. One child with PHHI who had not had pancreatectomy was also assessed. Standard endocrine assessment, pancreatic magnetic resonance imaging (MRI), and detailed direct and indirect tests of exocrine pancreatic function were performed.

Results—Pancreozymin-secretin stimulation test results were normal in only one child, borderline in two, and deficient in four, one of whom requires daily pancreatic enzyme supplements. Pancreoalyser tests performed in three children were borderline in two and abnormal in the other. Only one child had low faecal chymotrypsin values. One child developed insulin dependent diabetes at 9 years and two children at 1.0 and 13.3 years require diazoxide to maintain normoglycaemia. MRI showed no major regrowth of the pancreatic remnant after resection (n = 5).

Conclusions—Clinical evidence of endocrine or exocrine dysfunction has developed in only two patients to date, but detailed pancreatic function testing suggests subclinical deficiency in all but one of our patients with PHHI. Although 95% pancreatectomy results in postoperative control of blood glucose, subclinical pancreatic insufficiency is present on long term follow up and development of diabetes mellitus and exocrine failure remain ongoing risks.

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Keywords: nesidioblastosis; pancreatic function; persistent hyperinsulinaemic hypoglycaemia of infancy

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is a rare condition of inappropriate and excessive insulin secretion from β cell hyperplasia of the pancreas. Infants usually present within the first few hours or days of life with jitteriness, irritability, sweating, and fits, although presentation can occur weeks and months after birth. Non-ketotic refractory hypoglycaemia produces brain damage unless effective treatment is instituted at an early stage.

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 If these measures fail, surgical resection of the pancreas should be considered. 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.

The extent of resection is controversial although most paediatric surgeons now regard a 95% resection as the operation of choice.5 Lesser procedures result in a higher failure rate and the need for further pancreatic resection,6–7 but may result in a lower incidence of diabetes mellitus and exocrine failure. More radical resections may logically produce better postoperative glycaemic control, may reduce the risk of mental retardation, and may avert the need for further surgery—although these speculations have not been borne out by follow up studies.8–9 Recently, several authors have shown that by puberty the vast majority of children with PHHI who have undergone pancreatic resection will have developed insulin dependent diabetes.10–11 It has been hypothesised that the abnormal histological appearance of the β cell at the time of presentation may represent delayed fetal maturation of the pancreas. The hyperinsulinaemic state then resolves as β cell maturation occurs through childhood and subsequent β cell failure represents the end stage of PHHI.

Surgical resection and puberty may accelerate this failure process.10 Recent work on a mouse knockout model of PHHI has shown neonatal hypoglycaemia but with subsequent hyperglycaemia and hypoinsulinaemia as a result of a high frequency of apoptotic β cell death in these adult mice.12

This study aimed to investigate in detail the pancreatic exocrine and endocrine function of children with PHHI after pancreatic resection. An additional child who was managed solely by medical treatment was also investigated.

Subjects

All children referred to the Leeds General Infirmary during the past 18 years for surgical management of PHHI were contacted. In total there were 12 children: one died in the post-
Table 1  Patient details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Birth weight (g)</th>
<th>Gestation (weeks)</th>
<th>Age at operation (years)</th>
<th>Pancreatectomy (%)</th>
<th>Length of time after surgery at investigation (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3700</td>
<td>39</td>
<td>0.5</td>
<td>90</td>
<td>8.26</td>
</tr>
<tr>
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<td>5200</td>
<td>41</td>
<td>0.1</td>
<td>95</td>
<td>4.2</td>
</tr>
<tr>
<td>3</td>
<td>2020</td>
<td>35</td>
<td>0.4</td>
<td>95</td>
<td>1.9</td>
</tr>
<tr>
<td>4</td>
<td>3400</td>
<td>41</td>
<td>0.1</td>
<td>95</td>
<td>1.7</td>
</tr>
<tr>
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<td>4800</td>
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<td>0.1</td>
<td>95</td>
<td>0.9</td>
</tr>
<tr>
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<td>3400</td>
<td>41</td>
<td>2.2</td>
<td>85</td>
<td>12.7</td>
</tr>
<tr>
<td>7</td>
<td>4600</td>
<td>41</td>
<td>—</td>
<td>—</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Table 2  Clinical outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diabetes mellitus</th>
<th>Pancreatic enzyme supplementation</th>
<th>Current medication</th>
<th>Mental retardation</th>
<th>Gastrostomy/jejunostomy feeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>Nil</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>No</td>
<td>Carbamazepine</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>No</td>
<td>Nil</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Yes</td>
<td>Pancreatin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>Diazoxide</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>Insulin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>No</td>
<td>Diazoxide</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>


diagnostic period from sepsis (1984); one has since moved out of the region; and four did not give consent for investigation; the remaining six patients were involved in this study. We also traced one child (patient 7) who was managed medically without recourse to surgery and who was willing to participate. Median gestational age was 41 weeks (range 35–41), and median birth weight 4600 g (range 2020–5200), which placed four of the seven children above the 97th centile for weight at birth. There were five girls and two boys. Median age at pancreatic resection was 91 days (range 26 days to 2.2 years). Median age at the time of the pancreatic function study was 4.3 years (range 1.0–14.9) (table 1).

Methods

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 at −70°C 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; product numbers 718211, 159697, and 1005006, respectively). Elastase was assayed by a commercially available ELISA method (Schebo-Tech GmbH, Wettenberg, Germany).

PANCREATIC IMAGING

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

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 the United Leeds NHS Teaching Hospitals Trust. Parents received full written information sheets on the nature of the study as did the children where appropriate. Fully informed written consent was obtained.

Results

Of the 13 children who have had PHHI over the past 18 years, 12 were managed surgically, with one death in the postoperative period. A 95% pancreatectomy was undertaken in all children with PHHI after 1990. Before this date, lesser resections were done as this was considered to be the best procedure at that time. No child required a further pancreatic resection because of postoperative hypoglycaemia. Six of the children were available for detailed study of pancreatic function together with an additional child who had not undergone surgery (table 1). Of these seven children (table 2), two continue to require diazoxide to prevent hypoglycaemia; one is nearly 12 months on from a 95% pancreatectomy (patient 5) and the other is 13 years old and has not had a pancreatic resection (patient 7). One child has developed insulin dependent diabetes requiring Mixtard 20/80—18 units in the morning and 8 units in the evening (weight 57 kg). Two children still require gastrostomy/jejunostomy supplementary feeds to maintain blood glucose concentrations. One child takes 1 capsule of Creon (pancreatin; Duphar, Southampton, UK) with meals because of steatorrhoea and another has intolerance of fatty foods, causing diarrhoea, but is not on enzyme supplementation. Two children have severe developmental delay and fits—one underwent 95% pancreatectomy at 26 days of life (patient 2) because of intractable hypoglycaemia and the other child did not undergo pancreatic resection (patient 7).
Pancreatic exocrine and endocrine function after pancreatectomy

Table 3 Pancreozymin-secretin test results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Volume (ml/kg/test)</th>
<th>Chymotrypsin (µg/kg bw/test)</th>
<th>Amylase (IU/kg bw/test)</th>
<th>Lipase (IU/kg bw/test)</th>
<th>Elastase (µg/kg bw/test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3</td>
<td>98</td>
<td>7.0</td>
<td>16.6</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>4.2</td>
<td>1293</td>
<td>54.4</td>
<td>407.5</td>
<td>45.3</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>30</td>
<td>0.9</td>
<td>3.2</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>240</td>
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<td>6.1</td>
</tr>
<tr>
<td>5</td>
<td>2.2</td>
<td>726</td>
<td>17.6</td>
<td>257.0</td>
<td>37.7</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>110</td>
<td>8.6</td>
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</tr>
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<td>1.3</td>
<td>5347</td>
<td>187.8</td>
<td>221.2</td>
<td>95.4</td>
</tr>
</tbody>
</table>

Range 0.1–4.2 30–5347 0.9–187.8 3.2–407.5 0.4–95.4

Reference range 1.2–7.5 350–2700 90–1050 300–5000

Pancreozymin-secretin stimulation tests (table 3) showed slightly decreased amylase activity in one child (patient 2); slightly decreased lipase activity in one (patient 7); decreased lipase and amylase in one (patient 5); and frankly abnormal test results in the four other children, including the child on pancreatic supplements and a girl with fatty food intolerance. The other two children did not have steatorrhoea or evidence of malabsorption. We also measured duodenal juice elastase activity although there are as yet no available normal values for children.

Fat soluble vitamin concentrations were generally within the lower limit of the normal reference range although four children had subnormal vitamin A concentrations (table 4). Clotting studies were all normal. Despite the fact that faecal chymotrypsin has been considered the best non-invasive test of pancreatic insufficiency, only one child had a value below the normal reference range in agreement with her very abnormal pancreozymin secretin test. Interestingly, patient 7 who did not have pancreatic resection showed the highest faecal chymotrypsin value and duodenal juice amylase, chymotrypsin, and elastase values.

Three of the children (patients 1, 2, and 4) had 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 4.2, 3.0; 5.2, 6.0; and 4.2, 4.0 respectively.

MRI and ultrasound imaging of the pancreas visualised only small remnants of pancreatic tissue in the region of the head of the pancreas around the common bile duct consistent with an 85–95% pancreatectomy (fig 1), apart from patient 7 who had not had pancreatectomy. Significant pancreatic regeneration could not be shown in any of the children, although immediate postoperative scans were not available for comparison. Ultrasonography of the pancreatic remnant yielded less detailed images of the pancreatic remnant than MRI.

Discussion

The diagnosis of PHHI must be considered in any infant with refractory hypoglycaemia. Early diagnosis and appropriate treatment is imperative to prevent hypoglycaemic injury to the neonatal brain. Some infants, especially those presenting after the first few months of life, may be more receptive to medical interventions alone and successful medical treatment in up to 75% of cases has been reported. A significant proportion of children will, however, require surgical resection of the pancreas to control the hyperinsulinaemia. Two extensive reviews of the literature on surgical resection for PHHI spanning the years 1934–76 and 1977–87 have addressed the controversy about the extent of pancreatectomy. The first review showed an overall mortality rate of 10% and an incidence of 54% mental retardation in survivors. Eighteen per cent of patients undergoing < 90% pancreatic resection required further pancreatic resection. In the second series of 165 neonates, one quarter underwent 95–98% pancreatectomy with a mortality of 2.4% (one death) and an overall mental retardation rate of 12.5%; only 4.8% (two patients) required a further pancreatic resection. This compared with a 28% reoperation rate in the other three quarters having less than a 95% pancreatectomy. From this and other studies, a so-called 95% pancreatectomy is generally accepted as the surgical treatment of choice. Postmortem examinations of the pancreas...
Pancreatic exocrine function has not been previously studied in detail in children who have had a pancreatic resection for PHHI. The studies that table 5 summarises have generally defined pancreatic exocrine failure in terms of clinical requirement for pancreatic enzyme supplementation. Overall, only 5% of children were taking pancreatic enzyme supplements—10% of those after 95% pancreatectomy and 6% of those after 75–90% resection. We have shown from the pancreozymin secretin tests that all of our children have subclinical exocrine insufficiency and it is likely that they will all ultimately develop 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, but it is interesting to note that our 13 year old pubertal girl, who had not had surgery, recorded the highest enzyme activity, other than lipase, of all the children.

The aetiology of PHHI has still not been fully determined and more than one cause is possible. In 1994 a “PHHI gene” was localised to chromosome 11,20 and later that same year mutations in the sulphonylurea receptor (SUR) gene were implicated.30 31 The SUR, a subunit of the β 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 were possible to modulate activity of the SUR medically it may offer an alternative to surgical intervention. Not only would this negate the need for complex pancreatic surgery but it may also postpone or prevent the progression to end stage β cell failure. In vitro studies indicate that calcium channel blockers may be able to reversibly block insulin secretion from the β cells of patients with PHHI,32 and this may allow the development of new therapeutic strategies in this disabling condition. However, the transgenic mouse model of hyperinsulinaemia suggests that β cell maturation and premature death may be inevitable in PHHI,32 and our study supports this. It is important to be aware of the possible development of pancreatic failure in children with PHHI and investigate pancreatic function regularly.

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