Growth and endocrine function after near total pancreatectomy for hyperinsulinaemic hypoglycaemia

Ashraf T Soliman, Issa Alsalmi, Assim Darwish, Maurice G Asfour

Abstract
Seven children, with a mean (SD) age of 4·6 (2·1) years, who as infants (21 (7·5) days) underwent near total (95–98%) pancreatectomy for persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) were studied. At birth all the infants were macroscopic. Four infants had been born after a difficult labour, of whom three had moderate birth asphyxia and respiratory distress. All had normal thyroid function. After surgery transient hyperglycaemia was manifest in six of the children and required insulin treatment for 3·8 (3·8) weeks, and transient hypoglycaemia was encountered in one child and responded well to increased carbohydrate intake and diazoxide for three weeks. Six of the children rapidly crossed their length and weight centiles during the first year after surgery. At the end of the first year these children were at or below the 5th centile of height and weight for their age and gender. After a period of 4·6 (2·1) years, their mean (SD) height score was −2·57 (0·5), growth velocity 3·9 (0·75) cm/year, and growth velocity SD score −2·1 (0·55) these were significantly low and denoted significant growth retardation. The growth hormone peak responses to provocation with clonidine were normal (13·5 (2·8) μg/l). However, the circulating insulin-like growth factor-I (IGF-I) concentrations were significantly decreased (79 (34) ng/ml). Three of the children developed diabetes at two and a half, five, and seven years after surgery, two others had impaired oral glucose tolerance and six out of the seven children had an impaired C-peptide response to glucagon. Defective insulin secretion in these children might directly inhibit IGF-I synthesis in the liver. The body mass index of the pancreatectomised children was 14·9 (0·5) and was normal for age and gender; they had a normal 72 hour faecal fat content and normal serum albumin concentration. These data indicated grossly inadequate exocrine pancreatic function. It appears that children requiring near total pancreatectomy for PHHI have normal developmental milestones but defective linear growth with impaired insulin secretion and low IGF-I production despite normal growth hormone response to provocation.

Keywords: persistent hyperinsulinaemic hypoglycaemia of infancy, growth, growth hormone, insulin-like growth factor-I.

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) or ne Solidologie is the mainstay of the medical management through inhibition of glucose stimulated insulin secretion. Somatostatin inhibits insulin release; however, tolerance may develop and growth hormone secretion is suppressed. The most important aim of continuous treatment, the prevention of hypoglycaemia with subsequent irreversible brain neurodevelopmental impairment, cannot be reliably avoided by conservative treatment. Therefore, surgical treatment is becoming increasingly important.

In the majority of patients surgical resection involves a subtotal (85–90%) pancreatectomy. The reduction of hormone producing tissue resolves hyperinsulism. 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 hypoglycaemia. In comparison 28%
of patients undergoing subtotal pancreatectomy required a second operation compared with 5% of patients with 95–98% pancreatectomy. A primary 99% resection was performed in six patients with no recurrence. A 95% resection is claimed to produce the best overall results. Spitz et al reported short term borderline or low exocrine pancreatic function in most of the infants after 95% pancreatectomy. Three out of their 21 patients had evidence of steatorrhoea and two had intolerance to fatty food, whereas two children required pancreatic exocrine supplementation. However, long term exocrine pancreatic function after 95% resection appeared to be grossly normal in another study.

While the short term utility of pancreatectomy has been established (that is, hypoglycaemia is resolved), little information is available about its long term effects. These include growth and development in relation to the endocrine and exocrine pancreatic functions. To clarify this issue, we studied growth and developmental parameters and some endocrine functions of seven children who as infants underwent near total (95–98%) pancreatectomy.

Patients and methods

Seven children, two girls and five boys, with a mean (SD) age of 4-6 (2-1) years, who as infants underwent near total (95–98%) pancreatectomy (complete resection of the tail and pancreatic head leaving less than 5% of pancreatic tissue around the common bile duct) were the subjects of this study after obtaining parents’ consents. Their anthropometric data at birth (table 1) revealed significant macrosmosis. Four infants had difficult labour of whom three had moderate degree of birth asphyxia (Apgar score below 7 and five minutes after birth) and respiratory distress. All had normal thyroid function. Symptomatic non-ketotic hypoglycaemia was recorded during the first 12 hours after birth with blood glucose concentrations below 1 mmol/l in all the children. The concomitant serum insulin concentration during hypoglycaemia ranged between 10 and 44 μIU/ml (mean 30 (13-6) μIU/ml) and the mean C peptide concentration of 7-8 (4-3) μg/l. Medical treatment was tried first using diazoxide 20 mg/kg/day given at eight hourly intervals, glucagon, and hydrochlorothiazide as well as continuous infusion of glucose at a rate 17–25 mg/kg/min. This treatment was not successful to bring up the blood glucose concentrations to 2-6 mmol/l or above. The mean age at surgery was 21 (7-5) days. Transient hyperglycaemia occurred in six out of the seven children after surgery and required insulin treatment for 2–11 weeks (mean 5-8 (3-8) weeks), and transient hypoglycaemia was encountered in one child which responded well to increased carbohydrate intake and diazoxide and disappeared in three weeks. Histopathology proved a diffuse nature of the lesion in five children and focal head (1) and body (1) in the other two cases.

The patients with PHHI were followed up regularly in the paediatric endocrinology clinic, Royal Hospital, Muscat, every four to six months. Twenty age matched children with insulin dependent diabetes mellitus (IDDM) and 150 age matched normal Ommani children served as controls for growth data. Informed consent was obtained from the parents of all children included in the study. Each clinic visit children were examined with special emphasis on nutritional and growth data and their anthropometric measurements including weight, height, and head circumference recorded. Parents’ height was recorded and midparental height calculated. Harpenden calipers and anthropometric measurements were used. The data recorded were the average of three sequential measurements determined. The height SD scores were calculated according to the formula height SD score=(X1–X2)/SD, where X2 and SD are age matched population mean height and SD respectively and X1 is the subject height. Normal population data were according to ‘Tanner and Whitehouse. The body mass index (BMI) was calculated according to the formula BMI=weight (kg)/height (m²). The height growth velocity cm/year was calculated for the whole year and growth velocity SD scores recorded. Dietary evaluation, both qualitative and quantitative, was assessed by the dietitian for the pancreatectomised children using the recall method. The growth data of the three children who developed IDDM were recorded for a year after starting insulin treatment. Developmental assessment was carried on every six months. This included evaluation of the gross motor, manipulation (fine motor), speech/language, general understanding, and miscellaneous abilities according to Illingworth. The visual-motor assessment

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anthropometric data of children with PHHI before and after pancreatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No</td>
<td>Sex</td>
</tr>
</tbody>
</table>
| 1 | M | 51 | 54 | 1.56 | 35 | 7.7 | 70.8 | 1.94 | 43.3 | 2.7 | 87.8 | 1.94 | 47.5 | 2.5 | 9.2 | 2.5 | 3.8 | 1.2 | 14.4 | IDDM | 0.6
| 2 | M | 4-7 | 53 | 1.56 | 35 | 7.6 | 70.9 | 1.75 | 43.8 | 2.7 | 87.8 | 1.75 | 49.8 | 2.5 | 9.2 | 2.5 | 3.8 | 1.2 | 14.4 | IDDM | 0.6
| 3 | M | 4-5 | 53 | 1.56 | 34 | 8.0 | 68.4 | 2.02 | 42.5 | 2.7 | 9.9 | 2.02 | 46.2 | 3.1 | 11.1 | 3.1 | 3.5 | 1.2 | 14.4 | IDDM | 0.6
| 4 | M | 4-8 | 51 | 1.56 | 35 | 10.1 | 77.6 | 0.55 | 45.2 | 2.7 | 9.3 | 0.55 | 47.6 | 3.1 | 11.1 | 3.1 | 3.5 | 1.2 | 14.4 | IDDM | 0.6
| 5 | M | 4-5 | 49 | 1.56 | 35 | 8.3 | 69.9 | 2.42 | 44.7 | 2.7 | 9.3 | 2.42 | 47.6 | 3.2 | 11.3 | 3.2 | 3.5 | 1.2 | 14.4 | IDDM | 0.6
| 6 | F | 4-1 | 51 | 1.56 | 35 | 7.8 | 69.2 | 2.53 | 45.1 | 2.7 | 9.1 | 2.53 | 47.5 | 3.2 | 11.3 | 3.2 | 3.5 | 1.2 | 14.4 | IDDM | 0.6
| 7 | F | 4-1 | 51 | 1.56 | 36 | 8.0 | 68.4 | 2.14 | 45.5 | 2.7 | 9.3 | 2.14 | 47.6 | 3.2 | 11.3 | 3.2 | 3.5 | 1.2 | 14.4 | IDDM | 0.6
| Mean | 4-5 | 52 | 0.79 | 40 | 0.79 | 35 | 8.2 | 70.7 | 0.79 | 44 | 9.4 | 70.7 | 0.79 | 47.4 | 4.07 | 12.6 | 4.07 | 14.4 | IDDM | 0.6
| SD | 0.3 | 1-6 | 0.47 | 0.7 | 0.76 | 2.98 | 0.69 | 1.02 | 3.3 | 1.04 | 0.61 | 3.3 | 1.04 | 0.61 | 1.4 | 2.44 | 9.2 | 0.49 | 0.52 | 0.27 |

*IGT = impaired glucose tolerance, LCP = low C peptide response to glucagon, NL = normal. C peptide response and glucose tolerance.
included Gesell figures and the Goodenough-Harris draw a person tests. The bone age was determined according to Greulich and Pyle atlas. Glycated haemoglobin concentrations were estimated after pancreatectomy for hyperinsulinaemic hypoglycaemia.

Pancreatectomised children were investigated for their endocrine status. On the morning of the test a fasting (eight hour overnight fast) venous blood sample was obtained for determination of complete blood count and serum albumin, bilirubin, alkaline aminotransferase, alkaline phosphatase, calcium, phosphorus, and bicarbonate concentrations. The serum was separated from the formed elements by centrifugation and kept frozen at −20°C until analysed for growth hormone, free thyroxine, thyroid stimulating hormone, and insulin-like growth factor-I (IGF-I). An oral dose of clonidine (0·15 mg/m²) and intravenous dose of 0·5 mg tetracosactrin (Synacthen, Ciba) were given and blood samples were collected every 30 minutes for two hours for determination of growth hormone and cortisol concentrations. Human growth hormone and IGF-I were measured by radioimmunometric assay, employing reagents purchased from the Nichols Institute (San Juan Capistrano, CA, USA). Intra-assay coefficient of variation averaged 5·5% in the range of growth hormone values detected and 8·7% in the range of IGF-I concentration measured.

Free thyroxine, thyroid stimulating hormone, and cortisol concentrations were measured using Amerlex-RIA kits (Kodak Clinical Diagnostics). Glycated haemoglobin was measured by the IMx glycated haemoglobin assay (a boronate affinity binding assay) kits (Abbott Laboratory Diagnostic Division). The normal range for the non-diabetic population is 4·4–6·4%. After three days on full carbohydrate diet and after an overnight fast, an oral glucose tolerance test was performed (1·75 g glucose/kg body weight) and serum glucose estimated by glucose oxidase method before and one and two hours after the oral glucose load. On the second morning serum C peptide was determined before and six minutes after intravenous injection of 15 µg/kg glucagon. Exocrine pancreatic function was assessed by 72 hour stool fat estimation.

Statistical analyses were done using the unpaired t test to compare mean analyte concentrations among the study groups when data were normally distributed and Wilcoxon test when they were not. Statistical significance was accepted at p<0·05. Data are presented as mean (SD).

Results

Table 1 summarises the anthropometric data of patients and controls. Despite their large size at birth, six out of the seven children with PHHI crossed down growth centiles for length and weight during the first year after pancreatectomy to be at the 5th centile or below. After 4·6 (2·1) years of follow up their height SD score was significantly low at −2·57 (0·5) denoting statural growth impairment (figure) and significantly lower than midparental height SD score. Their mean annual growth velocity (3·9 (0·75) cm/year and growth velocity SD score (−2·1 (0·55)) were significantly low. Their mean BMI at 14·88 (0·6) was not different from those for the healthy controls, 15·8 (0·4).

Developmental evaluation, at a mean age of 4·6 (2·1) years, revealed that only one child had mild mental retardation with delayed motor and language development. The other six patients had normal gross and fine motor development. Their language development and cognitive function were appropriate for their age.

Table 2 represents growth data of pancreatectomised children in comparison with 20 children with IDDM and 150 normal children followed up for one year. The height SD score, annual growth velocity, and growth velocity SD score of pancreatectomised patients as well as their circulating IGF-I concentrations were significantly lower than those for children with IDDM and for the laboratory normal range for healthy children between 1–6 years (195 (37·5) ng/ml). The glycated haemoglobin concentrations were significantly higher in the pancreatectomised and IDDM groups compared with the normal range of the laboratory data for children between 1–6 years (4·6 (0·5%)).

At the age of 4·6 (2·1) years all children with PHHI had normal haemogram and hepatic, renal, and thyroid functions. Serum albumin concentrations did not differ between patients (41 (5·2) g/l) and controls (42·5 (6·3) g/l). Growth hormone peak response to clonidine provocation (13·5 (2·8) µg/l) was appropriate in all pancreatectomised children. Their basal (3·95 (0·59) nmol/l) and tetracosactrin provoked (845 (245) nmol/l) serum cortisol concentrations were normal. An oral glucose tolerance test showed a diabetic curve in three and impaired glucose tolerance in two out of the seven patients. The other two children had normal glucose tolerance. However the C peptide response to intravenous glucagon was impaired in six out of the seven patients (table 3).

Despite a history of intolerance to fatty meals in two out of the seven patients, exocrine pancreatic function as assessed by 72 hour stool collection was within the normal range (mean fat 6·1 (0·6) g/day; normal 2–7 g/day).
physiology. Circulating with the macrosomia in decline, after birth dramatic  
However, the regulation of hormones such as thyroxine, and is essential  
by acting on liquor insulin concentrations or by cordocentesis.35 36 Intrauterine macrosomia can be predicted by ultrasonic evaluation of different fetal anthropometric parameters.37 38  
Despite macrosomia at birth, six out of the seven infants rapidly crossed down growth centiles for length and weight. By the end of the first year their length and weight was at or below the 5th centiles for age and gender. The endocrine control of growth in utero is quite different from that after birth. Major growth promoting hormones such as growth hormone, thyroxine, and sex steroids have almost no influence on fetal growth.39 In contrast, insulin is essential for fetal growth by acting as mitogen on embryonic tissues40 and via stimulation of tissue IGF-I release.41 IGF-I controls organ growth and functional differentiation during fetal growth.42 43 These facts explain macrosomia in our children with nesidioblastosis as well as in infants of diabetic mothers. However, after birth dramatic changes occur with the appearance of a quite different physiology. Circulating insulin concentration declines, and IGF-I secretion becomes growth hormone dependent and less dependent on insulin.39 44 These changes, in addition to the switch off hyperinsulinaemia, with or without hypoinsulinaemia, after pancreatectomy might explain in part the rapid deceleration of growth in our children with PHHI during the first year after surgery. In support of this view, all our patients (numbers 2, 3, and 5) who were evaluated during the first year after surgery had impaired glucose tolerance and defective C peptide release after glucagon (peak C peptide 0·3, 0·68, and 0·85 ng/ml respectively). The possibility of compromised nutrition due to defective exocrine pancreatic secretion, especially during the few months after surgery, and its negative effect on IGF-I synthesis cannot be ruled out.44  
Infants of diabetic mothers who do not have exocrine pancreatic deficiency also show catch-down growth in the first year of life.45 In these infants poor feeding is a major problem that is often present and might be an important factor contributing to slowing of growth in these infants. Moreover, after major surgery the protein catabolic status might adversely affect growth especially during infancy. Recently this catabolic status has been prevented by administration of growth hormone/IGF-I treatment.47 48  
Dietary assessment during the first year after surgery, using the recall method for three days, revealed that six out of the seven infants had a normal appetite and consumed an adequate amount of milk and other food items (cereals, egg, vegetables, and meat/kg). Only one infant had severe anorexia and poor weight gain after the operation that necessitated gavage feeding for 10 days and pancreatic extract supplementation for eight weeks. During childhood they had grossly normal exocrine pancreatic function evidenced by normal 72 hour faecal fat excretion and their dietary intake was qualitatively and quantitatively normal. However, two children had a history of intolerance to dietary fat.  
At a mean age of 4-6 (2-1) years height SD score, growth velocity, and growth velocity SD score were significantly low. Decreased IGF-I synthesis in these children can explain in part their impaired statural growth. IGF-I production is regulated mainly by growth hormone,49 but other hormones including insulin as well as the nutritional status contribute to this regulation.50 51 Despite the possibility of ischaemic/hypoxic insult to the hypothalamic-pituitary axis during difficult labour and/or one or more of the hypoglycaemic seizure attacks, our patients have a proper growth hormone response to clonidine provocation, thus ruling out growth hormone deficiency. Their low basal and glucagon provoked C peptide

Table 2 Growth data of pancreatectomised children compared with normal children and those with IDDM; values are mean (SD)  

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (years)</th>
<th>Height SD score</th>
<th>Growth velocity (cm/year)</th>
<th>Growth velocity SD score</th>
<th>BMI (kg/m²)</th>
<th>Glycated haemoglobin (IGF-I) (ng/ml)</th>
<th>Bone age delay (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDDM (n=20)</td>
<td>5·7 (2-6)</td>
<td>1·5 (0-45)*</td>
<td>5·3 (0·12)*</td>
<td>0·85 (0·28)</td>
<td>15·6 (0·38)</td>
<td>8·25 (1·2)*</td>
<td>1·45 (0·21)</td>
</tr>
<tr>
<td>Normal (n=150)</td>
<td>6·3 (1-7)</td>
<td>0·99 (0·12)</td>
<td>6·6 (0·16)</td>
<td>0·21 (0-04)</td>
<td>15·8 (0·43)</td>
<td>4·6 (0·5)*</td>
<td>ND</td>
</tr>
<tr>
<td>Pancreatectomised (n=7)</td>
<td>4·6 (2-1)</td>
<td>2·57 (0·50)</td>
<td>3·9 (0·75)*</td>
<td>2·10 (0·55)*</td>
<td>14·9 (0·50)*</td>
<td>6·1 (1·5)*</td>
<td>1·20 (0·35)*</td>
</tr>
</tbody>
</table>

ND = not done.  
*p<0·05 IDDM/pancreatectomised groups v normal children.  
†Normal laboratory data for children between 1–6 years.

Table 3 Laboratory data of pancreatectomised children and normal children; values are mean (SD)  

<table>
<thead>
<tr>
<th>Pancreatectomised children (n=7)</th>
<th>Normal (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free thyroxine (pmol/l)</td>
<td>14·5 (2·0)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mIU/l)</td>
<td>1·03 (0·25)</td>
</tr>
<tr>
<td>Growth hormone (µg/l)</td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1·50 (0·45)</td>
</tr>
<tr>
<td>Peak</td>
<td>13·5 (2·8)</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>79 (34)*</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>395 (59)</td>
</tr>
<tr>
<td>Peak</td>
<td>845 (245)</td>
</tr>
<tr>
<td>C peptide (ng/ml)</td>
<td></td>
</tr>
<tr>
<td>0 Min</td>
<td>0·65 (0·35)*</td>
</tr>
<tr>
<td>6 Min</td>
<td>1·05 (0·50)*</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>0 Hours</td>
<td>7·4 (1·8)*</td>
</tr>
<tr>
<td>2 Hours</td>
<td>9·0 (3·6)*</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>41·0 (5·2)</td>
</tr>
</tbody>
</table>

*p<0·05.
Table 4 Growth data of the three diabetic children before and after insulin treatment

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Growth velocity (cm/year)</th>
<th>BMI (kg/m²)</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Growth velocity (cm/year)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>134</td>
<td>2.4</td>
<td>8.1</td>
<td>2.5</td>
<td>134</td>
<td>2.4</td>
<td>8.1</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>144</td>
<td>2.6</td>
<td>7.3</td>
<td>3.5</td>
<td>144</td>
<td>2.6</td>
<td>7.3</td>
</tr>
<tr>
<td>3</td>
<td>4.5</td>
<td>154</td>
<td>2.8</td>
<td>6.5</td>
<td>4.5</td>
<td>154</td>
<td>2.8</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*p<0.05 before vs after insulin treatment.

concentrations (6/7) and the high incidence of impaired glucose tolerance (2/7) and diabetes (3/7) denoted a state of hypoinsulinism that can impair hepatic IGF-I production. Moreover, insulin plays an important part in determining the bioavailability of IGF-I through its action on insulin-like growth factor binding protein-I (IGFBP-I). Therefore, defective insulin secretion can increase hepatic production of IGFBP-I leading to decreased bioavailability of IGF-I. In support of this view our patient (4), who experienced transient hypoglycaemia after surgery and had normal glucose tolerance and normal C peptide release after glucagon, had better linear growth than those with impaired glucose tolerance and/or defective C peptide release. Moreover, after one year of insulin treatment in the three children who developed IDDM, the growth velocity and height SD score improved significantly (table 4). In agreement with our findings, Glaser et al noted the occurrence of diabetes at puberty in children who underwent partial pancreatectomy as neonates. Although other studies reported normal pancreatic endocrine function along with ultrasonographic evidence of extensive regeneration of the pancreas after resection, in these studies the follow up period was too short to allow detection of late pancreatic abnormalities. However, the fact that control children with IDDM and higher glycated haemoglobin concentrations had better linear growth and significantly higher levels of circulating IGF-I compared with our pancreatectomised children denotes that other factors might contribute to their growth impairment. The normal BMI, serum albumin, and faecal fat concentrations and adequate dietary intake in all the pancreatectomised children indicate adequate exocrine pancreatic function and exclude any significant contribution of malabsorption and/or malnutrition in the production of their growth impairment and low IGF-I production.

Whereas the exocrine tissue grew adequately enough to prevent the development of significant malabsorption, the growth of the endocrine tissue was inadequate to maintain long term normal glycaemic control (3/7 with IDDM, 2/7 with impaired glucose tolerance, and 6/7 with impaired C peptide response to glucagon). The deterioration of glucose homeostasis seems to be progressive, as demonstrated in two of our children who had defective C peptide release and impaired glucose tolerance at seven and nine months after surgery and developed diabetes at the age of 2-5 and 5 years respectively. In support of our findings, Brockenbrough et al described discordance of exocrine and endocrine growth after 90% pancreatectomy in rats, and Bonner-Weir et al demonstrated defective glucose induced insulin release in rats after pancreatic regrowth after partial pancreatectomy. Leibowitz et al reported the occurrence of overt diabetes during puberty in six out of eight patients who underwent subtotal pancreatectomy as infants for PHHI. By comparing their results with ours it appears that near total pancreatectomy, a more extensive procedure, is followed by early onset of diabetes as the regrowth of the remaining β cell mass was adequate to maintain normal glycaemic control for only a few years (2-7) after surgery. Moreover, it is still questioned whether β cell failure is the natural end stage of PHHI, with the onset of diabetes being hastened by partial pancreatectomy and its extent.

Several authors have stressed the high incidence of mental retardation in children with PHHI, which is related to the delay in making the diagnosis and extreme difficulty experienced in controlling the hypoglycaemia. Developmental parameters, including motor, cognitive and language, were appropriate for age in six out of the seven patients. This could be explained on the basis of early diagnosis and early and extensive surgical management of our patients. However, one child has mild mental retardation, delay in both motor and language development, and grand mal epilepsy. Computed tomography of his brain at the age of 3 days revealed moderately dilated ventricles, wide cerebrospinal fluid spaces, and generalised low density involving all the cortical lobes. Repeated computed tomography of his brain at the age of 10 weeks, six weeks after pancreatectomy, showed deep cortical sulci and dilated ventricles consistent with cerebral atrophy. These early brain changes might be explained by his low Apgar scores (2 and five minutes (4 and 6 respectively) and/or by his severe and early hypoglycaemia. Experimental designs showed that energy failure and loss of ion homeostasis during hypoglycaemia are associated with cessation of electroencephalographic activity, which is followed by neuronal damage. The incrimination of a subtype of excitatory amino acid receptor, the N-methyl-D-aspartate (NMDA) receptor, in the pathogenesis of hypoglycaemia induced selective neuronal necrosis and the demonstrated usefulness of NMDA antagonists to prevent neuronal necrosis during hypoglycaemia impose the possibility of pharmacotherapeutic intervention.

In summary, in children who undergo near total pancreatectomy for PHHI the regrowth of the β cell mass appears to be inadequate for maintaining long term glycaemic control, with a high incidence of impaired glucose tolerance and IDDM during childhood. This defective insulin secretion appears to be an important cause of their impaired statural growth; however, their neurodevelopmental outcome is satisfactory.


Surgery for drooling

Drooling is said to be a problem in between 10 and 37% of children with cerebral palsy. It is messy, often unsightly, and sometimes smelly. It causes chronic irritation of facial skin, adds to the burden of care, and may cause embarrassment and loss of self-esteem.

The ins and outs of surgical treatment have been debated for some years. Surgical options include, alone or in combination, removal of salivary glands, ligation of salivary ducts, transposition of salivary ducts, and division of salivary gland nerve supply.

In Victoria, Australia, the favoured procedure has been transposition of the submandibular ducts into the tonsillar fossae and ligation of one parotid duct (Kerri-lyn Webb and colleagues, Developmental Medicine and Child Neurology 1995; 37: 755–62).

Thirty nine patients underwent the operation: 31 with cerebral palsy, four with neurological impairment of other cause, and four with intellectual disability without motor impairment.

Judging solely by preoperative and postoperative measures of drooling the results over six years of follow up were good with between 77 and 100% of patients showing improvement on various measures. Nevertheless 38% had ‘moderate to severe’ or worse drooling after the operation and in only 23% was postoperative drooling absent or mild. Twelve patients said that surgery had not helped them. Eighteen said their saliva had become thicker and 20 frothier and some found this distressing. There may have been an increase in dental caries and minor infections after the operation and five patients needed further surgery for ranulas. Nine complained of a dry mouth with crusting of the lips and two had airway obstruction leading in one to intubation and admission to intensive care.

In the same issue of Developmental Medicine and Child Neurology there is an editorial written by the president of the American Academy for Cerebral Palsy and Developmental Medicine calling for better outcome assessments and including the statement, ‘We must listen to our patients to determine the kinds of outcomes that are important to improve the quality of their lives’. Yes, indeed.
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