Management of secondary diabetes mellitus after total pancreatectomy in infancy

S A GREENE, A AYSLEY-GREEN, G SOLTESZ, AND J D BAUM

University Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford

SUMMARY We report five children who required total pancreatectomy in the neonatal period for life threatening hypoglycaemia. Subsequent diabetes was managed with once daily subcutaneous insulin, oral pancreatic extract, and a controlled carbohydrate diet. Daily home blood glucose profiles in four of these children were different from those of 14 C-peptide negative children with type 1 insulin dependent diabetes—in the pancreatectomy group there was less variation in blood glucose throughout the day with a fall after breakfast as against a rise after breakfast in the type 1 group. Hyperglycaemia (greater than 10 mmol/l) with or without ketonaemia was extremely rare in the pancreatectomy group. Despite neonatal convulsions, physical growth and development have been normal. Hypoglycaemia, usually after food refusal, has been a major problem. In addition, there have been considerable emotional and family disturbances despite the excellent metabolic control, which presumably reflect the cumulative difficulties in managing such young children with diabetes.

Type 1 insulin dependent diabetes mellitus occurs infrequently in infancy. Total pancreatectomy is an even rarer cause of carbohydrate intolerance and the optimal clinical management of this secondary diabetes has not been defined. We report our experience with five children who underwent total pancreatectomy when aged less than 1 year to control severe non-ketotic hyperinsulinaemic hypoglycaemia due to nesidioblastosis of the pancreas.

Patients

All five infants (three boys, two girls) were born at term with a mean birthweight of 4.1 kg (range 3.6 to 4.5 kg). They were identified as having severe non-ketotic hypoglycaemia within two days of birth and hyperinsulinism was confirmed subsequently.¹ Treatment with diazoxide and chlorothiazide was introduced without success. All children initially underwent partial pancreatectomy in an unsuccessful attempt to alleviate severe persistent hypoglycaemia; subsequently total pancreatectomy was performed at a mean age of 6.4 months (range 3.5 to 9.5 months) (see Fig. 1). Histology of the excised pancreas showed a diffuse abnormality of the endocrine tissue consistent with nesidioblastosis.²

Results

Immediate postoperative period. All five children required insulin within three hours of total pancreatectomy because of the development of progressive hyperglycaemia with accompanying osmotic diuresis. During the first 48 hours after the operation an insulin infusion of 0.1 units/kg/hour was required together with a glucose infusion of 2 to 3 mg/kg/minute to maintain blood glucose between 5.0 and 7.0 mmol/l. This was in contrast to the pre-operative glucose requirement of greater than 16 mg/kg/minute to maintain a blood glucose concentration of above 2.0 mmol/l. Enteral feeding with milk formula was started when the intestinal ileus had resolved and pancreatic enzyme substitution was provided in the form of Pancrex in a dose of 50 mg of powder given with each 100 ml of formula.

Insulin was given intravenously until enteral feeds were completely established. In four infants a change was then made to intermittent subcutaneous injections of a short acting insulin preparation, given three to four times daily depending on the blood glucose measurements. Three days later these infants were changed to subcutaneous injections of an intermediate acting insulin given once daily. One infant was managed differently and transferred from intravenous insulin to a continuous subcutaneous

Fig. 1 Summary of the timing of total pancreatectomy and subsequent insulin treatment in five children with hyperinsulinism secondary to nesidioblastosis of the pancreas.

insulin infusion of a short acting insulin preparation, using a portable insulin pump. In this child normoglycaemia was maintained over the next 12 days. When the infant established total oral feeding she was changed to an intermediate acting insulin preparation given as a single daily injection.

Long term management. The subsequent insulin treatment of these children is summarised in Fig. 1. All children have been managed on subcutaneous insulin injections of an intermediate acting preparation given once daily. The individual insulin requirement (units/kg body weight) has remained stable since total pancreatectomy; over the cumulative total experience of 18 years the mean daily insulin requirement has been 0.71 units/kg (range 0.67 to 0.74).

The parents of all five children received the usual dietary advice given for insulin dependent diabetes

mellitus in childhood.³ In all five children, however, clinical hypoglycaemia has been a frequent problem occurring up to several times a week and usually during the day. This has nearly always been attributed to the omission or refusal of meals. Two children were admitted to hospital on several occasions because of food refusal. Growth in all five children has been normal, following the expected centiles for height and weight.

Four of the five children had neonatal hypoglycaemic convulsions (see Table). Three suffered further convulsions up to 6 months of age. Two children have subsequently suffered occasional, brief, generalised convulsions, sometimes (but not always) associated with hypoglycaemia or fever; these two children remain on anticonvulsant treatment. Nevertheless the neurophysical development in all five children has been normal, although three of them have noticeable if relatively mild behaviour disorders.

Diabetic control. Long term diabetic control using home blood glucose monitoring. (Dextrostix and Glucometer; Ames division, Miles Laboratories) was evaluated over a period of one to three months for four children (cases 1 to 4). Measurements were performed on a programmed basis consisting of a minimum of one test daily staggered on successive days, thus building up a 24 hour blood glucose profile. The mean 24 hour blood glucose profile for these children is shown in Fig. 2. No comparable data on other diabetic children under the age of 5 years was available from our clinic since most diabetic children of this age are reluctant to perform routine blood glucose monitoring over a similar period. We therefore compared the blood glucose profile seen in the pancreatectomy children with a mean 24 hour blood glucose profile obtained using an identical home blood glucose monitoring programme in 14 C-peptide negative diabetic children (age range 11.0 to 17.7 years) monitored during a trial comparing human with porcine monocomponent insulin.⁴ The profile, obtained using an intermediate and short acting porcine preparation, is shown in Fig. 2; the mean insulin requirement was 0.84 (range 0.68 to 1.19) units/kg/24 hours and each

Table Summary of neurological problems in five children with secondary diabetes mellitus after total pancreatectomy

Case No	Neonatal period	Subsequent history	Treatment	Development
1	Convulsions	Febrile convulsion	Carbamazepine	Normal
2	Convulsions (mild)	Hypoglycaemic fit		Normal
3	'Near miss cot death': convulsions	Febrile convulsions	Sodium valproate	Normal
4	Convulsions; apnoea			Normal
5	Hypoglycaemic fit	Hypoglycaemic fit		Normal

Fig. 2 Comparison of 24 hour blood glucose profiles in four children with diabetes secondary to total pancreatectomy and in 14 C-peptide negative insulin dependent diabetic children.

Each point represents the mean of at least 10 blood glucose estimations from each child.

child was studied over a three month period. In both groups every effort was made to optimise blood glucose control.

The mean 24 hour blood glucose profile of the children with diabetes secondary to pancreatectomy was different to that of the children with type 1 juvenile diabetes. The characteristic after breakfast peak blood glucose concentration in the latter group was absent in the pancreatectomy group—by contrast a fall in blood glucose at this time was often found among the pancreatectomy children. The pancreatectomy children showed a mean fall in blood glucose of 0.8 mmol/l while the type 1 diabetic children showed a mean rise of 0.9 mmol/l. Furthermore the blood glucose concentrations in the pancreatectomy group approximated more closely to the physiological range throughout the 24 hour period. Given the small numbers and the fact that the groups cannot be compared, direct statistical comparison of the profiles cannot be made.

None of the pancreatectomy children has required hospital admission for hyperglycaemia and ketosis. Home monitoring of urine for ketones has shown ketonuria to be exceedingly rare, even during intercurrent infections.

Discussion

This report describes five children with diabetes

mellitus secondary to total pancreatectomy in infancy. They seem to exhibit some unusual characteristics in comparison with children with type 1 juvenile diabetes. The resistance to hyperglycaemia and ketonaemia is striking and similar to that seen in adults with diabetes secondary to pancreatectomy.⁵⁻⁸ Moreover, their blood glucose profiles differed from those of a group of C-peptide negative diabetic children (children with type 1 diabetes devoid of residual endogenous insulin) in that the rise in blood glucose after breakfast, so evident in type 1 diabetes, was absent despite similar prescriptions of insulin and diet.

It is possible that the absence of other pancreatic hormones after total pancreatectomy contributes to the relative stability of blood glucose concentrations in these children. For example loss of the normal glucagon response to a mixed protein carbohydrate meal, a physiological mechanism for maintaining normoglycaemia in the healthy non-diabetic subject,⁹ may account in part for the fall in blood glucose concentrations after breakfast. It is, however, less clear how the absence of pancreatic polypeptide and somatostatin may affect blood glucose regulation.¹⁰ A further factor that may be relevant to the apparent resistance to hyperglycaemia is the increased insulin sensitivity associated with an increased concentration of insulin receptors on peripheral cells, which has recently been described in adults with post-pancreatectomy diabetes.¹¹ Furthermore, pancreatic exocrine deficiency and its correction by pancreatic extract introduces other variables in the regulation of blood glucose values through alterations in intestinal digestion.

The approach to the dietary management of the patients has been the same as for other diabetic children: a relatively liberal carbohydrate diet (45 to 50% energy from carbohydrate sources) high in dietary fibres and whole foods. In view, however, of the apparent fall in blood glucose concentrations after breakfast the dietary regimen may require revision.

The home blood glucose monitoring which has been successfully used in all these families has proved to be of value in this group of children, particularly for the identification and management of hypoglycaemia. The frequent heel and finger pricks have been tolerated well by the children from earliest infancy with no short term complications of the procedure, although some scarring of the heel pads is evident on close examination.

The most difficult clinical problem we have experienced with these children has been food refusal at times when the blood insulin values were at their highest. In two children this was so severe as

to require intravenous glucose infusion for several days on more than one occasion. It is interesting to note that the children were subjected to prolonged periods of gavage feeding as babies and they showed an apparent lack of interest in sucking and swallowing when oral feeds were introduced. Despite this their growth has been normal.

Neurological development has been relatively normal despite neonatal hypoglycaemic convulsions in all five children and further convulsions in later infancy in three children—associated with fever and in two with hypoglycaemia. Despite the normal physical and neurological development there have been behavioural difficulties in four children. These emotional problems together with the original organic disease and subsequent management of diabetes have contributed to family disturbances consisting of noticeable parental anxiety and depression, marital strain and, in one family parental separation.

Total pancreatectomy is a major procedure not to be undertaken lightly in infancy particularly in the knowledge that it will lead to secondary diabetes mellitus. In these five children it was judged to be justified in view of persistent life threatening hyperinsulinism with the associated risk of severe hypoglycaemic brain damage. Despite the difficulties encountered in the management of young children with diabetes, however, their growth is normal and they are free from obvious neurological and developmental abnormalities. Moreover their unusually stable blood glucose control allows for some optimism in terms of life long good health and freedom from diabetic microvascular disease. Long term supervision and evaluation will be needed to establish whether or not this proves to be the case.

We thank Drs P Swift, D Johnston, and A Piesowicz for allowing us to report their patients; Sister Sally Strang and Mrs A Smith for their help and advice; and Miss Sue Ruddock for typing the manuscript. S A G is a Novo Research Fellow and G S is a Smith & Nephew Fellow.

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Correspondence to Dr S Greene, University Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Received 9 January 1984