Short Reports

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Islet-cell Tumour Causing Hypoglycaemia in a Newborn Infant

Hypoglycaemia due to islet-cell tumour is rare in children, and there have been few reports of its occurrence in newborn infants. Cases in which tumours were found *post mortem* have been described by Scholten and Van der Vegt (1960), Bernheim *et al.* (1961), and François *et al.* (1962). More recently, Salinas *et al.* (1968) and Garces, Drash, and Kenny (1968) described 2 infants with persistent hypoglycaemia which was relieved by resection of islet-cell tumours several weeks after delivery. 2 further infants with congenital islet-cell tumours have been briefly reported by Drash *et al.* (1968) and Mann, Rayner, and Gourevitch (1969).

We wish to describe a further infant with an islet-cell tumour which caused severe hypoglycaemia soon after birth.

Case Report

The patient was a girl born at term weighing 4.1 kg. 2 hours after delivery she had a cyanotic attack, and her blood sugar was subsequently found to be less than 10 mg./100 ml. 2-hourly feeds with added carbohydrate were given, together with intravenous infusions of glucose and fructose, but her hypoglycaemia persisted and she was transferred to this hospital at the age of 5 weeks. On admission she was an obese, unresponsive infant. Her weight was 4.8 kg., her length 53 cm., and her head circumference 38.5 cm. No focal neurological signs were found, but occasional myoclonic jerks were seen.

Her treatment after admission is shown in the Fig. Attempts to control her hypoglycaemia by means of frequent feeding (8 g. SMA, Wyeth, and 4 g. carbohydrate, 2-hourly) were unsuccessful, and treatment with increasing doses of diazoxide (up to 20 mg./kg. per day) and chlorothiazide (15 mg./kg. per day) was given. As her hypoglycaemia persisted, and as she was sensitive to l-leucine (see below), her dietary leucine was restricted to 100 mg./kg. per day. This measure was also ineffective and she continued to have brief convulsions which could be rapidly controlled by giving glucose through a naso-gastric tube. Though she gained 2 kg. in 9 weeks, there was no change in her head circumference and she showed little evidence of mental development.

When she was 14 weeks old, laparotomy was carried out by Mr. H. H. Nixon. As the pancreas appeared and felt normal, partial pancreatectomy was performed. An islet-cell tumour was subsequently found in the resected tissue (see below). On the day after operation she appeared more alert and her convulsions stopped. On the 7th post-operative day her wound required re-suture, and healing was subsequently delayed by infection. However, her general condition continued to improve, and 6 weeks after operation her motor and social behaviour were appropriate for her age. At the age of 32 weeks her mental development was normal, her head circumference had increased to 44 cm., and her electroencephalogram (Dr. G. Pampiglione) showed a minimal excess of slow activity but no focal or paroxysmal features. One brief convulsion occurred 13 days after operation but she has had no further fits.

Blood sugar and serum insulin. Serial blood sugar (glucose-oxidase method) and serum insulin (Grant, 1968) estimations were made before and after operation. Blood sugar and serum insulin were also estimated after giving l-leucine (150 mg./kg.) by nasogastric tube or glucagon (20 µg./kg.) by intramuscular injection.

The serial blood sugar results before and immediately after operation are shown in the Fig. Many values

FIG.—Serial blood sugar values before operation (90–120 minutes after a feed) and during the early post-operative period (4 hours after a feed). The periods of treatment with diazoxide, chlorothiazide, and a restricted leucine diet are also shown.

below 50 mg./100 ml. were obtained 90–120 minutes after a morning feed during the period of treatment with diazoxide, chlorothiazide and a low leucine diet. During the first 3 days after operation the values ranged from 228 mg./100 ml. to 395 mg./100 ml. Subsequent blood sugar values 4–8 hours after a feed ranged from 47 mg./100 ml. to 87 mg./100 ml.

Before operation, serum insulin levels between 25 μ U/ml. and 37 μ U/ml. were obtained at times when the blood sugar was less than 50 mg./100 ml. After operation, insulin values between 2 μ U/ml. and 10 μ U/ml. were obtained 8 hours after a feed.

The results of the leucine and glucagon tests are given in the Table. Before operation, leucine provoked a

histological changes (Crigler, 1962). In others, islet-cell tumours or generalized islet-cell hyperplasia (Haddad *et al.*, 1962) were found.

Differentiation between insulinoma and a generalized β cell abnormality may be difficult as leucine sensitivity may be present in either condition (Haddad *et al.*, 1962; Garces *et al.*, 1968). The clinical features of the present case suggested that hypoglycaemia was due to excessive insulin secretion. Though the laboratory findings confirmed this impression, they were not considered diagnostic of insulinoma, and uncertainty as to the cause of hyperinsulinism led us to start treatment with diazoxide. This drug has been used in the management of a number of children with hypoglycaemia, either alone or in combination with a thiazide, and has been found to inhibit leucine-induced insulin secretion in children with leucine-sensitive hypoglycaemia (Baker *et al.*, 1967). However, treatment with diazoxide was unsuccessful in 3 infants with congenital islet-cell tumours (Salinas *et al.*, 1968; Garces *et al.*, 1968; Drash *et al.*, 1968). It was also ineffective in the present case, and it appears that failure to respond to diazoxide may be almost a diagnostic feature in infants with islet-cell tumours.

Failure of diazoxide therapy in our patient, together with clear evidence of hyperinsulinism, left little choice other than surgical treatment. After removal of her tumour she showed a remarkable improvement. Though it is still too early to assess whether she has completely escaped the neurological sequelae of severe hypoglycaemia, she showed rapid developmental 'catch up' after operation and her head began to grow. Similar improvement was noted in the cases described by Salinas *et al.* (1968) and Garces *et al.* (1968), and it has been suggested that the late prognosis after removal of an insulinoma is better than that in other forms of infantile hypoglycaemia (Crigler, 1962).

Summary

The clinical features of an infant with an islet-cell tumour are described. Hypoglycaemia, which began 2 hours after delivery, failed to respond to treatment with diazoxide, chlorothiazide, and a low leucine diet but was relieved by removal of the tumour at the age of 14 weeks. Rapid developmental 'catch up' occurred after the operation.

We wish to thank Dr. G. H. Newns for allowing us to publish this case report; Dr. A. G. Hesling for referring the patient; and Dr. Barbara Clayton and her staff for the blood sugar and serum insulin determinations.

TABLE

Serum Insulin and Blood Sugar Levels during Leucine and Glucagon Tests Performed a Week after Admission and 6 Weeks after Operation; Pre-operative Tests Begun 90 minutes after Feed and Post-operative Tests 4½ hours after Feed

Time From Leucine or Glucagon (min.)	Before Operation		After Operation	
	Serum Insulin (μ U/ml.)	Blood Sugar (mg./100 ml.)	Serum Insulin (μ U/ml.)	Blood Sugar (mg./100 ml.)
(a) Leucine				
– 30	45	17	7	51
– 5	24	12	8	56
+ 15	98	3	11	47
+ 30	128	2	12	35
+ 45	—	—	9	26
+ 60	—	—	7	34
(b) Glucagon				
– 30	18	35	13	59
– 5	—	13	9	57
+ 15	160 +	45	17	107
+ 30	—	64	18	138
+ 45	29	24	20	136
+ 60	25	14	15	109

profound fall in blood sugar and an excessive rise in serum insulin (Grant, 1968). Injection of glucagon was followed by a very high serum insulin value.

Pathological findings. The specimen of resected pancreas appeared normal but when sectioned after fixation, an ovoid, sharply circumscribed tumour (0.5 cm. $\times$ 0.5 cm. $\times$ 1.0 cm.) was found in the tail. This tumour was composed of cords and nests of cells which contained β granules (aldehyde-fuchsin stain) and which resembled normal islet-cells (Dr. P. Symchych).

Discussion

Though neonatal hypoglycaemia is usually transient, cases have been described in which severe hypoglycaemia persisted for weeks or months. In some of these the pancreatic islets appeared normal (Schwartz *et al.*, 1955) or showed only minor

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Suspending Agents in Medicaments as Possible Sources of Galactose to Galactosaemic Child

The need to exclude galactose from the diet of galactosaemic patients is well understood, and the difficulties of achieving this have been well documented. As little as 250 mg. lactose administered daily as a tablet excipient to a galactosaemic child has been reported sufficient to arrest weight gain (Bower and Smallpeice, 1955).

Tragacanth and acacia (gum arabic) are widely used as suspending agents in pharmaceutical liquid preparations; for example several of the BPC or

NF oral suspensions, and sulphadimidine paediatric mixture BNF. Both these gums, as well as carrageenan (Irish Moss) and agar, are used extensively in the food industry. All four are complex galactosides, and therefore potential sources of galactose. A galactosaemic child prescribed two suspensions concurrently for 6-hourly administration would receive 40 ml. of mixture equivalent to 500 mg. gum daily, in addition to intake from foods and confectionery products.

The purpose of our investigation was to find whether these compounds may be hydrolysed *in vivo* to free galactose.

Experimental Work

The concentrations of tragacanth, acacia, agar, and carrageenan used in the following experiments were those normally found in liquid pharmaceuticals and foods. In each experiment, products of hydrolysis were demonstrated by thin-layer chromatography.

(1) Each gum was heated with strong acid at 100 °C. for 4 hours. Products of hydrolysis were demonstrated on Silica Gel G absorbent using chloroform/acetic acid/water (6/7/1) as solvent and α -naphthol/sulphuric acid for visualization.

(2) Each material was incubated at 37 °C. with crude malt diastase (α - and β -amylase) for 2 hours.

(3) A solution of each gum was incubated with human salivary amylase together with a jejunal biopsy specimen of proven normal lactase activity. Each solution was adjusted to pH 6.5 in the presence of chloride ions (0.1%), and incubated at 37 °C. Controls of starch for α -amylase activity, and lactose for lactase activity were incubated to confirm suitable conditions for enzymic digestion.

(4) Solutions, and controls as above, were incubated with hog pancreatic α -amylase and human disaccharidase. Each tube was adjusted to pH 6.5, and incubated at 37 °C.

Several chromatographic systems were examined, and optimum separation was found with cellulose MN 300 as adsorbent 250 μ thick, and ethyl acetate/pyridine/water (2/1/2) as solvent. Using aniline phthalate for visualization, 0.5 μ g. galactose could be detected. This procedure was used in all experiments except (1).

Results

The results are shown in the Table.

It will be noted that free galactose was identified after strong acid treatment, and after digestion with β -amylase. This enzyme is not present in mammalian tissue but commonly occurs in plants and bacteria. Results from incubation with saliva and jejunal enzyme failed to demonstrate galactose after 24 hours, though both controls gave positive results when tested after 1 hour. Similarly, analysis of samples treated for 24 hours with