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Hyperinsulinism

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A 2-year-old boy had had severe intractable hypoglycaemia since birth. Transient success with diazoxide treatment delayed diagnosis until the age of 1 1/2 years. It was based on measurements of plasma insulin, blood glucose and urinary ketones at the end of a controlled fast, a normal glycaemic response to glucagon and an unusually high rate of glucose infusion necessary to maintain the blood sugar at a normal level. Subtotal pancreatectomy restored the blood sugar to normal without any impairment of exocrine pancreatic function.

The most common forms of neonatal hypoglycaemia such as that occurring in small-for gestational age infants and in infants of diabetic mothers, etc., are usually transient, lasting only a few days after birth. Persistent hypoglycaemia in the neonate or in the young infant is less common and usually results from inappropriate, excessive secretion of insulin or a deficiency of one of the hepatic glucoregulatory enzymes. This type of hypoglycaemia is often severe and intractable. Prompt recognition, specific diagnosis, and aggressive treatment are therefore essential to prevent central nervous damage.

Report of a case

The boy was born in a country hospital after an uneventful pregnancy of 40 weeks, weighing 3.2 kg. The 26 years old mother was healthy with no family history of diabetes, pancreatic teratoma, erythroblastosis, Beckwith-Wiedemann syndrome or leprechaunism. At 3 days of age, during breast-feeding the boy became cyanotic and limp, and had a blood glucose of 10 mg/dl. He was treated with an initial bolus of intravenous glucose followed by glucose infusion. This could be discontinued after a couple of days, and blood glucose levels remained normal between feedings from day 6 until discharge at 2 weeks of age.

Readmission was needed after 6 weeks, following clonic seizures, convulsions, eye rolling and profuse sweating at home. A glucose tolerance test revealed a glucose-disappearance rate (K_G) of 6.8% per minute. Glucagon and epinephrine tolerance tests were normal. Plasma insulin was 12 μU/ml in a random sample. He was put on long-term glucocorticoid and transfer-

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red to the metabolic unit of a hospital in Budapest.

There, plasma insulin levels of 4.6 and 7 μU/ml were measured in association with low blood glucose values; growth hormone and cortisol levels were normal. The liver was enlarged to 3 to 4 cm below the costal margin, but histology excluded glycogen storage disease. There was no metabolic acidosis and the levels of glucogenic amino acids were normal. An oral leucine tolerance test (100 mg/kg) was made at 5 months of age. The initial blood glucose of 42 mg/dl dropped to 22 mg/dl at 15 min and the child lost consciousness. A diagnosis of leucine-sensitive hypoglycaemia was made, hydrochlorothiazide and later diazoxide (10 mg/kg) treatment was started and the child was put on a low protein, high carbohydrate diet with frequent feedings. Hypoglycaemia recurred at one year of age despite 15 mg/kg diazoxide treatment, and frequent epileptiform convulsions were seen.

The patient was admitted to our Department at 1 1/2 years of age. He was 85 cm tall and weighed 12 kg, both within the normal range. Apart from a marked hypertrichosis no abnormal physical signs were detected; the liver was not enlarged. Bone age advancement of more than 1 year was noted probably due to the long-term diazoxide treatment. Psychomotor development was considerably delayed, he needed help to sit up and was unable to stand erect. Testing yielded an IQ of 49.

Diurnal blood glucose profile (Figure 1) revealed persistent hypoglycaemia with little improvement on high dose (25 mg/kg) diazoxide therapy. The urine was negative for ketone bodies and reducing substances. Blood pyruvate and lactate levels were normal.

Two intravenous glucose tolerance tests (1 g/kg body weight) revealed K_G values of 3.0 and 2.8% per min. The result of a continuous glucose infusion test is shown in Figure 2. An infusion rate of as high as 16.8 mg/min/kg glucose was needed to maintain normoglycaemia.

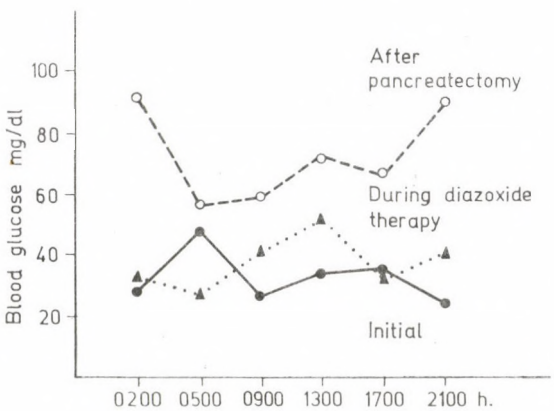

FIG. 1. Diurnal blood glucose profile

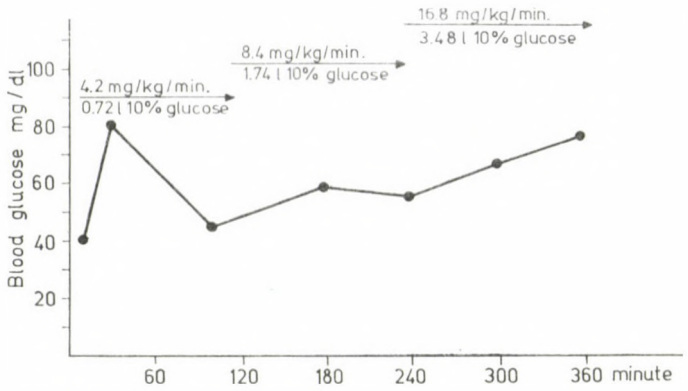

FIG. 2. Blood glucose levels during different rates of glucose infusion

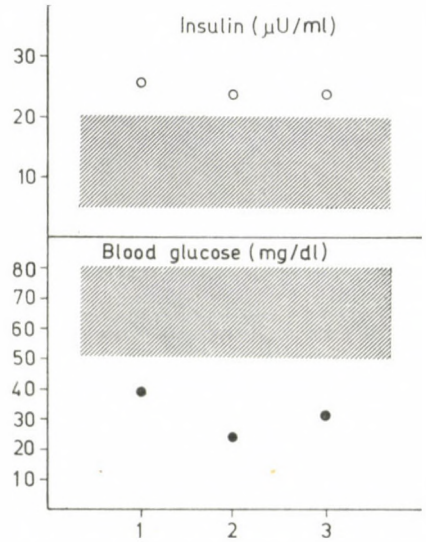

FIG. 3. Plasma insulin and blood glucose levels at the end of 3 fasting periods. (Shaded area represents the normal range)

Plasma insulin levels were not high during glucose and oral leucin tolerance tests. The result of the latter test was difficult to interpret because of the already low initial blood glucose value.

Simultaneously measured blood glucose and plasma insulin levels are shown at the end of 3 short fasting periods in Figure 3. Each plasma insulin concentration was elevated in relation to the blood glucose level. The lower levels of branched-chain amino acids (Table I) were regarded as a direct consequence of the hyperinsulinism [2].

Subsequently, after an unsuccessful trial with propranolol [3], pancreatic exploration was decided. Since no adenoma was found on inspection and

by palpation, a subtotal (85%) pancreatectomy was performed: the entire pancreatic tail and body and a considerable part of the head were removed.

TABLE I

Branched-chain amino acid levels in hyperinsulinism (μmol/l)

	First sampling	Second sampling	Controls (M ± SD)
Valine	115	192	232 ± 28
Isoleucine	43	55	69 ± 13
Leucine	60	137	134 ± 20

Histological sections of the pancreas stained conventionally with haematoxylin and eosin and aldehyde fuchsin showed no abnormality, no microadenoma, islet cell hypertrophy and hyperplasia or nesidioblastosis. The tissue was brittle and it was not possible to perform quantitative analysis of the immunoperoxidase stained material. The islets were normal and immunoperoxidase staining revealed normal

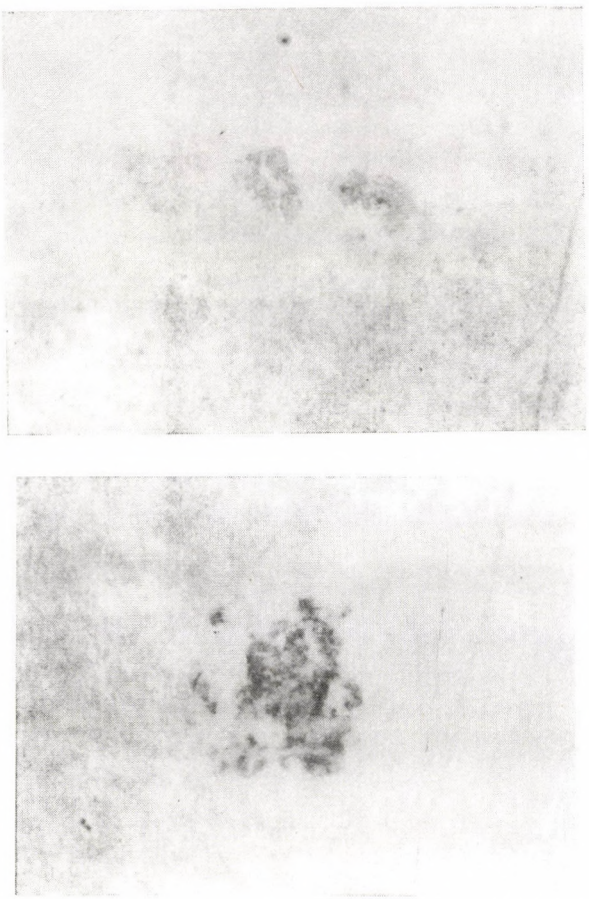

FIG. 4. Immunohistochemistry of the pancreas; *a)* insulin positive and *b)* glucagon positive cells

amounts of insulin positive cells. Staining for glucagon was of a good quality and indicated normal amounts of the hormone (Figs 4a, b). Immunoperoxidase staining for HPP showed scattered single positive cells typical of a "non-HPP" area.

Except for a transient hyperglycaemia during surgery, the blood glucose level remained normal. Fig. 1 shows the diurnal blood glucose profile 6 months after pancreatectomy. A blood glucose level of 61 mg/dl was measured at the end of a 12 h fasting period, with no detectable insulin and moderate ketonuria.

Exocrine pancreatic functions were normal and there was a considerable improvement of the psychomotor functions. Now the boy is able to stand and walk alone and speaks a few words. There is, however, no doubt that the recurrent and prolonged periods of hypoglycaemia have caused brain damage and mental retardation.

Discussion

Almost all cases of hypoglycaemia which persist beyond the neonatal period result either from an abnormality of hepatic glucose or amino acid metabolism or from hyperinsulinism. In fact, it has been shown that hyperinsulinism is the most common cause of severe persistent hypoglycaemia during the first year of life [15]. The specific diagnosis of hyperinsulinism is not an easy one. Simple measurement of plasma insulin level is not sufficient, since the excessive insulin secretion in organic hyperinsulinism does not always manifest itself with excessive concentrations of circulating insulin.

The most useful test for hyperinsulinism is a controlled fast [7], when the patient is fasted with close monitoring of the blood glucose until a level below 40 mg/dl is reached. Measurement of plasma insulin, free fatty acids and beta-hydroxybutyrate at this level of hypoglycaemia provides maximum diagnostic information.

Plasma insulin falls to very low levels during caloric restriction; values below 5 to 12 μU/ml are routinely noted under these circumstances. Consequently, insulin levels higher than 12 μU/ml in association with blood glucose levels below 50 mg/dl are distinctly abnormal.

In patients with hyperinsulinism the secretion of islet-cell hormones is disturbed, with an inability to shut off insulin release during periods of hypoglycaemia. Absolute values of immunoreactive insulin in these infants may be normal or even low but are inappropriately elevated in relation to the blood glucose level.

The usual leucine and tolbutamide tolerance tests are not as specific as in adults and frequently fail to reveal the hyperinsulinism.

Hyperinsulinaemia prevents lipolysis and ketogenesis which are the normal metabolic consequences of the counter-regulatory endocrine changes in reponse to a falling blood glucose concentration. Demonstration of non-ketotic hypoglycaemia in older infant supports the diagnosis of hyperinsulin-

ism [15], and this is also true for newborns [1]. Plasma ketone levels could not be measured in our patient but the failure to detect ketones in the urine during hypoglycaemia was a clear evidence of hypoketonaemia.

Glucose tolerance tests give variable results [5]. Because of the rapid recurrence of hypoglycaemia, a safer method of assessing glucose clearance was recommended [1], to calculate the rate of glucose infusion, in terms of mg/kg/mın, needed to maintain the blood glucose concentration above 40 to 50 mg/dl. Using this approach, it can be seen from Figure 2 that a glucose infusion rate higher than 15 mg/kg/min was needed to ensure a normal blood sugar level. This rate of infusion corresponds to 3500 ml of 10% glucose solution for 24 h, an excessive amount for a child of 12 kg, and two to four times the normal glucose production rate.

In the vast majority of the cases with hyperinsulinism, glucagon administration during hypoglycaemia caused an increase in blood glucose concentration. The glycaemic response to glucagon favours the diagnosis of hyperinsulinism: the excess insulin secretion appears to direct glucose to glycogen synthesis. The other hypoglycaemic conditions in infancy and childhood are related to starvation-like conditions with exhaustion of liver glycogen and a failure to increase the blood glucose concentration after glucagon.

A further indirect biochemical proof of hyperinsulinism is the low level of branched-chain amino acids (Table I). There is a significant inverse correlation between plasma insulin and branched-chain amino acid levels [2]. Branched-chain amino acids were elevated in diabetic ketosis (insulin-deficiency) and decreased in patients with insulinoma (insulin-excess). Suppression of insulin secretion by propranolol is a useful diagnostic and therapeutic test in malignant insulinoma [3], but has failed in our patient. Finally, somatostatin has been found to increase blood glucose concentration, possibly by inhibiting insulin secretion [10].

Thus, the most important diagnostic points for hyperinsulinism are [1],

an inappropriately elevated plasma insulin concentration for blood glucose values;

a glucose infusion rate of more than 15 mg/kg/min needed for maintaining the blood glucose level above 40 mg/dl;

low blood (and urinary) ketone bodies during hypoglycaemia, is the most simple and useful test; and, finally,

a glycaemic response to glucagon during hypoglycaemia.

Until recently, persistent hyperinsulinaemic hypoglycaemia has been attributed to a number of different conditions including isolated B-cell adenoma [17], diffuse B-cell hyperplasia [17], microadenomatosis [14], and "functional" B-cell disorders without histologic changes [13]. Since 1970 [4], a growing number of reports has drawn attention to the association of pancreatic nesidioblastosis with severe infantile hypoglycaemia, and now it is generally accepted [6, 11] that nesidioblastosis is the most com-

mon histological finding in this condition. The term indicates an abnormal differentiation of isolated pancreatic islet cells from blastic duct cells [12]. The histological criteria for nesidioblastosis are an increase in the total endocrine area, with ductular-insular proliferation and neoformation of discrete endocrine cells from ductal epithelium. There is also a decrease in the number of somatostatin cells and a loss of normal insulin and somatostatin cell ratio and contact. For reliable diagnosis, immunohistochemistry and morphometry are necessary. The lack of abnormality in the conventionally stained sections can lead to a histological diagnosis of "functional" B-cell disorder, but can also indicate an unrecognized nesidioblastosis.

In therapy, the immediate task is to increase the blood glucose concentration, to prevent convulsions and neurological damage. Glucose administration is clearly the first therapeutic measure, but even very high infusion rates only alleviate the symptoms. Most reports have emphasized the extreme difficulty in controlling the blood glucose level in these infants.

Hydrocortisone and glucagon are not effective for long [1], and the most effective drug available to inhibit insulin secretion is diazoxide. As in other cases reported in the literature, diazoxide had an initial beneficial effect in our patient with a subsequent recurrence of hypoglycaemia. The hyperglycaemic effect of diazoxide is enhanced by thiazide diuretics. This combination of therapy has also been tried in our case, but only with transient success.

Severe persisting hypoglycaemia resistant to drug therapy calls for pancreatectomy. Clearly, this is a major step and some caution is needed before proceeding to surgery.

If no adenoma is disclosed by careful inspection and palpation, subtotal pancreatectomy is indicated in which 75 to 85% of the pancreas is removed. A significant number of children have benefited from this form of therapy. Among the 63 children reported by Hamilton [8], 40 exhibited a complete remission, 7 did not improve, 1 died as a result of surgery, and 15 were considered to have a partial remission necessitating a reoperation or continued medical treatment to maintain a normal blood sugar. In our patient, partial pancreatectomy was sufficient to cure the hypoglycaemia, but it must be noted that a significant number of infants who had no adenoma [1, 16] remained hypoglycaemic after partial pancreatectomy and had to be submitted to total or near-total pancreatectomy.

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