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Hyperinsulinaemic hypoglycaemia in infancy and childhood: a practical approach to diagnosis and medical treatment based on experience of 18 cases

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Clinical and biochemical data are presented on 18 children with severe hyperinsulinaemic hypoglycaemia born to non-diabetic mothers. Thirteen presented within three days of birth, three by 20 months and two aged nine years. Diagnosis of hyperinsulinism (HI) was made in a single blood sample by showing inappropriate plasma insulin levels (23 ± 3 mU/l) for glycaemia (1.2 ± 0.1 mmol/l), with low blood ketone body, lactate, alanine and glycerol levels. All children showed increased glucose disappearance rates (KG $7.6\% \pm 0.06$) and glucose requirement (range, 9—25 mg/kg/min) and an exaggerated glycaemic response to glucagon when hypoglycaemic. Confirmatory tests included measurement of plasma insulin levels during leucine and arginine tolerance tests, during hypercalcaemia and after fish insulin. Coeliac angiograms were performed in three cases. Clinical progress could be divided into five categories. Four cases recovered normal insulin control spontaneously (transient neonatal HI); two children responded and remain on diazoxide therapy, two responded to diazoxide after partial pancreatectomy (diazoxide responsive HI); in three cases resolution of hypoglycaemia resulted from resection of isolated adenoma (insulinoma); total pancreatectomy was needed in five cases (nesidioblastosis) and two children were victims of drug administration (drug induced HI). This analysis allows the definition of a practical approach to diagnosis and management of this major clinical problem.

Hyperinsulinism (HI) causing severe persistent or recurrent hypoglycaemia is a rare medical emergency in childhood which presents specific diagnostic and therapeutic problems. The high incidence of brain damage and subsequent mental retardation is well-recognized [3, 8] and may be related to delay in making the diagnosis and to the difficulties of treating the hypoglycaemia.

The purpose of this paper is to review and summarize biochemical and hormonal studies and the experience gained in the management of 18 patients, in order to define a practical approach to diagnosis and treatment.

Patients

The data of 18 neonates, infants and children treated during the period from 1975 to 1982 were analysed. Six infants were inborn patients, the remainder were referred after varying degrees of assessment and treatment. Some aspects of the metabolic, endocrine and histological studies of six of these patients (Cases 1, 2, 3, 7, 11 and 16) have been published previously [3, 5, 7, 35].

For comparison of the biochemical and endocrine changes in hyperinsulinism with those in other forms of hypoglycaemia in

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TABLE I

Clinical course of 18 hyperinsulinaemic patients

Patient No	Sex	Gestational age (wk)	Birth weight (kg)	Age symptoms started	Symptoms	Surgery	Histology
Nesidioblastosis							
1	M	40	4.38	At birth	Jittery	Total pancreatectomy	NB*
2	F	38	3.65	4 hours	Floppy, feeding difficulty	Total pancreatectomy	NB
3	M	40	3.7	6 hours	Collapse, averted neonatal death	Total pancreatectomy	NB
4	M	41	4.41	11 hours	Jittery	Total pancreatectomy	—
5	F	38	4.5	2 days	Convulsions	Total pancreatectomy	NB
Insulinoma							
6	M	40	4.18	2 days	Cardiac arrest	Removal of adenoma	Insulinoma
7	M	38	4.20	9 weeks	Convulsions	Removal of adenoma	Insulinoma
8	F	38	3.5	9 years	Behaviour disorder	Removal of adenoma	Insulinoma
Transient Neonatal HI							
9	M	41	2.96	3 days	Cyanosis, tachypnoea	—	—
10	M	41	2.83	6 hours	Jittery	—	—
11	M	36	2.96	30 mins	Jittery	—	—
12	M	36	2.57	30 mins	Apnoea, hypotonia	—	—
Diazoxide-responsive HI							
13	M	40	3.33	10 weeks	Convulsion	Partial pancreatectomy	B-cell hyperplasia
14	F	36	2.25	6 months	Convulsion	—	Inconclusive
15	M	38	3.74	5 days	Convulsion	—	—
16	M	40	3.20	3 days	Cyanosis	Partial pancreatectomy	Inconclusive
Drug induced HI							
17	M	—	—	14 months	Coma	—	—
18	F	—	—	9 years	Convulsion	—	—

* NB Nesidioblastosis

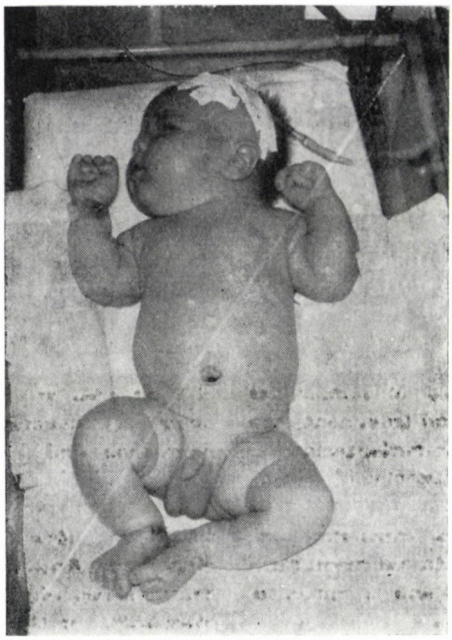

FIG. 1. Newborn infant with nesidioblastosis of the pancreas showing increased adiposity and resemblance to an infant of a diabetic mother

early life, data from five children with "ketotic" hypoglycaemia were also analysed. These children were aged between 1 and 6 years; one was suffering from glucocorticoid deficiency, the remainder from "accelerated starvation" [19].

The pregnancy in all mothers of hyperinsulinaemic neonates had been normal and none had glycosuria or rhesus incompatibility. None of the infants had the Wiedemann—Beckwith syndrome.

On the basis of pancreatic pathology, form of presentation, treatment and outcome, the patients can be grouped as shown in Table I, which contains some of the relevant clinical data of the patients.

Group I. Nesidioblastosis. All five infants in this group were large-for-dates newborns with a characteristic appearance of generalized adiposity, resembling the infants of diabetic mothers (Fig. 1).

Group II. Insulinoma. This group consisted of two infants and one child. Both infants were large-for-dates with the striking physical characteristics of the babies in Group I.

In none of the seven neonates in Groups I and II was the liver enlarged at birth, but all developed increasing hepatomegaly due to glycogen deposition [5] as massive amounts of glucose were infused to control the hypoglycaemia.

Group III. Transient neonatal HI. The common characteristic of the group was that hyperinsulinaemic hypoglycaemia never recurred after the first 8 weeks after birth. Cases 9 and 10 were born small-for-gestational age, the other two being appropriate-for-gestational age. Case 11 had an unusual course. His hypoglycaemia was successfully controlled by diazoxide during the first few days, but he then developed severe lactic acidosis which was effectively treated with dichloroacetate. Transient hyperinsulinaemic hypoglycaemia developed again after the correction of hyperlactataemia [7].

Group IV. Diazoxide-responsive HI. All infants in this group were born with a weight appropriate-for-gestational age, the symptoms of hypoglycaemia occurring over a wide age range.

Group V. Drug induced HI. Two children presented in severe hypoglycaemic coma at the age of 14 months and 9 years. Non-accidental administration of an oral sulphonylurea was confirmed by measurement of plasma and urine glibenclamide in

the former. In the latter, circumstances of the presentation and the subsequent biochemical evaluation made the diagnosis almost certain (vide infra).

Laboratory methods

Venous blood samples were withdrawn and immediately added to ice-cold 5% perchloric acid for assay of blood glucose and intermediary metabolites. Blood was also added to a heparinized tube for assay of plasma insulin and free amino acids. Plasma was stored at —20 °C until assayed. Levels of blood glucose, lactate, pyruvate, acetoacetate, hydroxybutyrate, glycerol and alanine were determined by standard enzymatic techniques [10]. Plasma insulin was measured by radio-immunoassay [1]. Individual free amino acids were separated and measured by automated ion-exchange chromatography using ninhydrin detection. Statistical significance was assessed by means of the Mann Whitney Rank Sum Test and the Student *t* test.

Results

Basal metabolite and hormone levels

Blood Glucose and Plasma Insulin Concentrations.

Mean blood glucose level at the time of diagnosing hypoglycaemia was 1.23 ± 0.07 mmol/l and mean plasma insulin level 23.3 ± 3 mU/l. There was no significant difference between the mean plasma insulin levels of newborns (26.0 ± 1.8 mU/l, n = 29) and infants (20.3 ± 2.5, mU/l n = 27) during hypoglycaemia.

The relationship between blood glucose and plasma insulin concentrations in our patients when hypoglycaemic and during normoglycaemia achieved by high rates of glucose infusion is shown in Fig 2 which also shows the normal relationship in the adult [39]. Plasma insulin concentrations for the level of glycaemia were inappropriately elevated. Some children had lower concentrations of plasma insulin which, although in the normal range for normoglycaemia, were inappropriate in the presence of hypoglycaemia.

Total Blood Ketone Body Concentrations (acetoacetate plus hydroxybutyrate). Associated with the inappropriately raised plasma insulin values, there were significantly lower

Table II

Gluconeogenic Substrates in Hyperinsulinism (mean ± SEM)

	Alanine (mmol/l)	Glycerol (mmol/l)	Lactate (mmol/l)	Pyruvate (mmol/l)
Newborns	0.34 ± 0.05	0.28 ± 0.01	1.62 ± 0.41	0.16 ± 0.03
n	3	2	6	6
Control*	0.48 ± 0.02	0.37 ± 0.02	2.90 ± 0.2	0.16 ± 0.01
n	24	24	24	24
p	<0.05	NS	<0.01	NS
Infants and children	0.19 ± 0.03	0.13 ± 0.01	0.97 ± 0.12	0.08 ± 0.01
n	11	3	11	11
Control	0.29 ± 0.02**	0.21 ± 0.01***	(0.5 ÷ 1.5)****	(0.5 — 0.15)****
n	12	28		
p	<0.01	<0.005		

* Stanley et al 1979 (36)
** Brodehl and Gellisen 1968 (14)
*** Persson and Gentz 1966 (32)
**** Normal range in our laboratory

concentrations of total blood ketones in both newborns and infants compared with controls (newborns: $0.13 \pm \pm 0.01$ mmol/l versus 0.25 ± 0.04 mmol/l, $p < 0.005$ [4]; infants and children 0.13 ± 0.01 mmol/l versus 0.21 ± 0.02 mmol/l, $p < 0.01$). [32]. Infants and children with HI showed

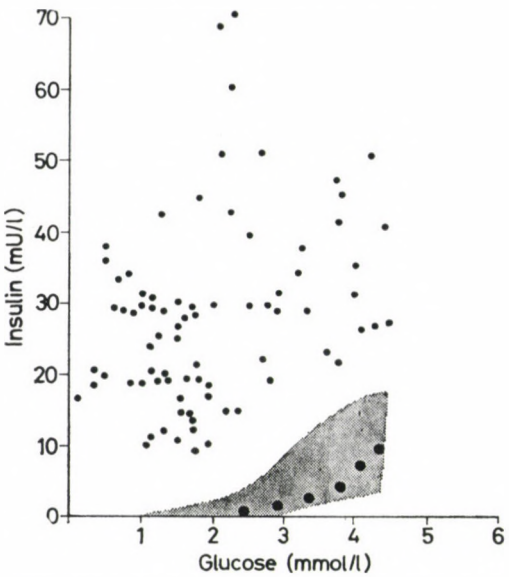

FIG. 2. Relationship between blood glucose and plasma insulin in infants and children with hyperinsulinism. Values shown were measured during fasting as well as during glucose infusions. The shaded area represents normal controls when normoglycaemic and after injection of fish insulin [39] ●——●: Case 18

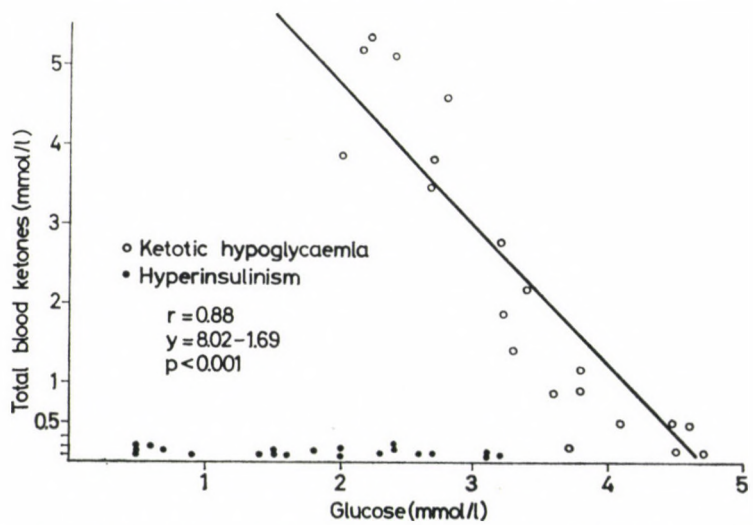

FIG. 3. Relationship between blood glucose and total blood ketone levels in hyperinsulinism and in ketotic hypoglycaemia

no increase in blood ketone levels with decreasing concentrations of blood glucose in contrast to the significant inverse correlation found in ketotic hypoglycaemic (Fig. 3) and normal children [37].

Blood Gluconeogenic Substrate Concentrations

Blood glycerol levels were significantly lower in HI infants as compared to normal controls and both HI infants and newborns had significant hypoalaninaemia (Table II). Neonates with HI had significantly lower mean blood lactate levels (Table II).

Branched-chain amino acid levels were measured in Case 16. Plasma valine, isoleucine and leucine concentrations were 0.121, 0.043 and 0.06 mmol/l, respectively, all markedly reduced compared with levels in normal fasting children [16].

TOLERANCE TESTS

Intravenous Glucose Tolerance Test. Intravenous glucose tolerance tests (0.5 g/kg bolus of glucose intravenously), were carried out in eight patients as part of the initial medical treatment. The glucose disappearance rate was abnormally rapid, the mean K_G value of 7.6 $\pm$ 0.9/min being four to six times the normal value [22]. Blood glucose dropped very quickly with rebound symptomatic hypoglycaemia in all cases requiring a glucose infusion for correction.

There was an inappropriate increase in plasma insulin for the low blood glucose concentrations in the basal samples before glucose administration, and although glucose caused further modest increases in some patients, the mean plasma insulin

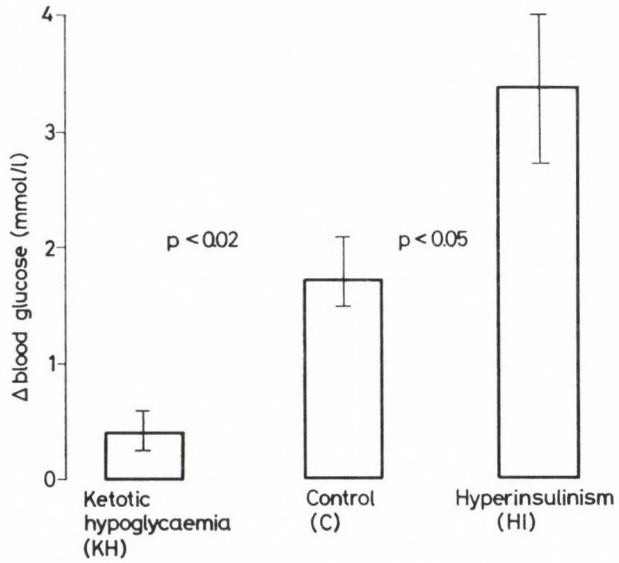

FIG. 4. Maximum glucose increment during glucagon (0.1 mg/kg intramuscularly) provocation test (mean$\pm$SEM)

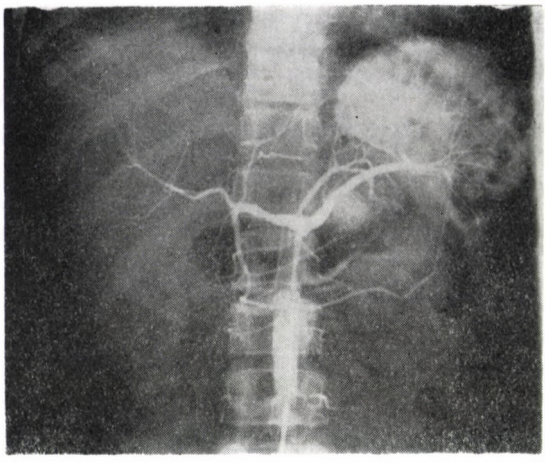

FIG. 5. Coeliac angiogram in a nine years old girl with isolated insulinoma in the tail of the pancreas (Case 8)

concentration did not change significantly throughout the test (basal plasma insulin 28 ± 5 mU/l, peak plasma insulin 46 ± 15 mU/l n = 8).

Glucagon Provocation Test. Fig. 4 shows the increase in blood glucose concentrations after the injection of glucagon (0.1 mg/kg intramuscularly) in eleven HI patients compared with the control data derived from Finegold et al. [23]. Values from blood samples drawn from five children with ketotic hypoglycaemia (KH) when hypoglycaemic at the end of a diagnostic provocative fast are also shown. Despite being hypoglycaemic, glucagon administration caused a highly significant increase in blood glucose concentration in children with HI, which was greater than that in control children ($p < 0.01$). In contrast, there was an insignificant glycaemic response to glucagon in the KH group. No significant change occurred in the mean plasma insulin level after the administration of glucagon in the hyperinsulinaemic patients (basal plasma insulin 36 ± 5 mU/l, peak plasma insulin 77 ± 24 mU/l, n = 4), although there was wide variation. Plasma insulin levels were not measured in the controls or in the KH children.

Other Diagnostic Tests

Oral leucine (100 mg/kg) was given to 5 patients. Although the mean blood glucose level did not change significantly, one patient developed profound symptomatic hypoglycaemia, associated with a moderate increase in plasma insulin from 25 to 32 mU/l.

Intravenous arginine (0.5 g/kg over 30 minutes) was given to Case 1, causing an increase in plasma insulin from 20 to 55 mU/l within 20 minutes and a fall in blood glucose from 2.5 to 1.1 mmol/l.

Calcium infusion [27] as a provocation test for hyperinsulinism was given to case 18; there was no change in blood glucose nor in plasma insulin. Measurement of endogenous insulin release during fish-insulin induced hypoglycaemia [39] was also performed in this child. The blood glucose concentration decreased after three injections of fish insulin (0.2 U/kg to 2.5 mmol/l), accompanied by a normal decrease of plasma insulin to 1.2 mU/l (Fig. 2) thus confirming normal control of insulin secretion (vide infra). These data supported our conclusion that presenting hyperinsulinaemic hypoglycaemia had been due to non-accidental ingestion of a sulphonylurea agent (vide infra).

Selective coeliac angiography was carried out in Cases 6, 8, 13 revealing an insulinoma in Case 8 (Fig. 5). No detectable pancreatic anomaly had been found in this patient by ultrasound prior to the coeliac angiogram. Both angiography and sonography were negative in Cases 6 and 13 despite the fact that an insulinoma was found subsequently at operation in the former.

Treatment

Intravenous glucose. Immediate correction of the presenting hypoglycaemia was achieved by giving a bolus of glucose (0.5 g/kg) intravenously followed by a continuous glucose infusion. The mean rate of glucose infusion required to maintain blood glucose levels above 2 mmol/l was 16.1 $\pm$ 2.1 mg/kg/min, considerably above the 4—6 mg kg/min required by normal neonates [11]. All the infants were given glucagon injections to prevent severe hypoglycaemia during the glucose infusions.

Diazoxide. Having demonstrated hyperinsulinism, the mainstay of medical therapy was diazoxide, given at 8 hourly intervals at a mean starting dose of 20 mg/kg/day and increasing to a maximum of 25 mg/kg/day. In most cases chlorothiazide was also given with diazoxide at a dose of 125 mg/day. No drug therapy was used in the two small-for-gestational age infants (Cases 9, 10) nor in Case 8, a child with an insulinoma demonstrated by angiogram. This child was subjected to immediate surgery.

Two children (Cases 14 and 15) responded and remained dependent upon diazoxide therapy; two responded to diazoxide only after partial pancreatectomy (Cases 13 and 16). Hypoglycaemia could not be controlled by diazoxide before resection of the adenoma in Cases 6 and 7, nor before and after partial pancreatectomy in nesidioblastosis: total pancreactomy was needed in all these five children.

Complications of diazoxide treatment. The appearance of facial and extrasexual hair of lanugo type (hypertrichosis lanuginosa) was observed in most cases treated for a period longer than a few months. Diazoxide was stopped after the development of heart failure and fluid retention in Case 4, and the dose was reduced after the development of hyperglycaemic ketoacidosis in Case 14.

Other forms of medical treatment. Addition of zinc protamine glucagon (0.1 mg/kg intramuscularly every 12 hours) to diazoxide and chlorothiazide had initial beneficial effects in Cases 1, 4 and 5, but recurrent hypoglycaemia developed after a few weeks despite increasing the dose and frequency of the glucagon.

Introduction of phenytoin [15] in Case 1 and propranolol [13] in Cases 1 and 6 did not improve the blood glucose concentration.

Normoglycaemia was restored with suppression of insulin secretion by a four hour infusion of somatostatin in Cases 7 and 15 [3], but this drug was not used as long-term treatment.

No consistent beneficial effect of hydrocortisone was evident [2].

A leucine free diet was tried in Case 16 in the referring hospital following a positive oral leucine tolerance test, but it failed to reduce the frequency of the hypoglycaemic attacks.

Finally, an unsuccessful attempt was made in Case 3 to provide an increase in alternative fuels to glucose by increasing blood ketone body concentrations by means of a diet rich in medium chain triglyceride [26] and by injections of growth hormone [21].

Surgical treatment. Surgical treatment is not discussed in detail, the summary is given in Table I. All five patients in Group I underwent total pancreatectomy. In Cases 6 to 8, a localised adenoma was found in the tail of the pancreas and removed. Partial pancreatectomy was performed in Cases 13 and 16. The pancreas of four of the five children in Group I had the histological appearance of nesidioblastosis, as defined previously [2, 12, 25, 33]. The remaining child, Case 4, had a near normal appearance. However, islets from this pancreas demonstrated abnormal glucose control of insulin release when incubated in vitro similar to the finding reported previously in Case 1 [5]. The pancreas from Cases 13, 14 and 16 were examined in referring hospitals by non-specific staining techniques, which preclude precise quantification of the endocrine cells.

The management of the children after total pancreatectomy has been outlined previously [5].

Psychomotor development

Fifteen of the 18 cases described had severe neonatal or infantile hypoglycaemia associated with recurrent convulsions. One of these patients, Case 11, had other associated metabolic abnormalities (metabolic acidosis and hyperlactataemia) and is excluded from this aspect of our review. The remaining 14 children have been assessed regularly and at an average age of 3.8 years (range 1 to 10 years), the majority (11 children) are developing normally; one is in the low normal range for IQ and only two are severely retarded with frequent fits. It is important to note that both were late referrals, diagnosis and appropriate treatment having been considerably delayed during which time they suffered long periods of repeated hypoglycaemic convulsions.

The incidence of severe brain damage in our cohort (15%) was better than that of previous studies [8, 2].

Discussion

Hyperinsulinism is the commonest cause of persistent hypoglycaemia in infants and children [for recent reviews see 8, 19, 30, 34, 41]. The majority of patients in this study developed severe symptomatic hypoglycaemia during the first few days after birth emphasizing the frequency of the condition in the neonatal period. The striking physical resemblance to an infant of a diabetic mother seen in many infants suggests prenatal hyperinsulinism. Most of the patients presented with the classical symptoms of hypoglycaemia but one infant (Case 3) presented as an averted neonatal death [6]. It is also salutory that one child (Case 8) was diagnosed after a one year history of convulsions and behaviour disorder, for which she had been referred to a child psychiatrist and paediatric neurologist.

The most important diagnostic point for hyperinsulinism is the demonstration of inappropriate plasma insulin values for the level of glycaemia. Insulin release normally falls to very low and undetectable levels when blood glucose concentration decreases [39] and the demonstration of even normal fasting levels of plasma insulin during severe hypoglycaemia implies a defect in the control of basal insulin release.

Insulin also inhibitis ketogenesis through a decrease in adipose tissue lipolysis and hence a diminution of fatty acid substrate supply to the liver [40].

The co-existence of hypoglycaemia and hypoketonaemia in HI is of major clinical significance. On the one hand the brain is deprived of glucose as a primary fuel whilst on the other hand ketone bodies are not available as alternative fuels. Thus the central nervous system appears to be left with no fuels available to maintain normal metabolism.

Insulin exerts regulatory control over gluconeogenesis by influencing the supply of gluconeogenic precursors reaching the liver [18, 38]. This explains the significant hypoalaninaemia, hypolactataemia and low glycerol levels in this study.

Finally, we have also confirmed the occurrence of low levels of branched-chain amino acids as has been reported previously [9, 16].

It follows that hyperinsulinism causes a specific and diagnostic profile of circulating homones and intermediary metabolite concentrations. The condition can be recognized in a single blood sample by showing hypoglycaemia with inappropriately elevated plasma insulin and low blood ketone body, glycerol and branched-chain amino acid concentrations. Almost all other causes of hypoglycaemia in childhood are associated with catabolism, as demonstrated by increased ketone body concentrations (so-called "ketotic hypoglycaemia"), glycerol and branched-chain amino acids together with low or undetectable plasma insulin values. This pro-

file is so characteristic as to make other diagnostic tests usually unnecessary. Some comments on other tests are, however, appropriate.

The high glucose disappearance rate can be regarded as one of the biochemical characteristics of hyperinsulinism. The diagnostic value of the glucose tolerance test, however, is limited by the danger of reactive hypoglycaemia, as shown by the fact that all our patients became severely hypoglycaemic during the test. Calculation of the glucose infusion rate in terms of mg/kg/min needed to maintain a blood glucose level above 2.0 mmol/l is a safer method of assessing glucose clearance.

An important and predictable effect of hyperinsulinism is the inappropriate conservation of liver glycogen during hypoglycaemia due to inhibition of liver glycogenolysis by insulin. This is clearly demonstrated by the large increase in blood glucose levels when glucagon was administered during hypoglycaemia.

The leucine tolerance test in our study was of little diagnostic value and we recommend caution in its use. The increased release of insulin after leucine may cause symptomatic hypoglycaemia, but if the initial glucose level is low (as in most patients with neonatal hyperinsulinism) the stimulatory effect of leucine on insulin release may not be evident.

The intravenous arginine provocation test, calcium infusion and fish insulin induced hypoglycemia were only used in single patients and further studies are needed to define the reliability of these tests. Nonetheless, these tests are occasionally indicated, as demonstrated in Case 18, a child subsequently shown to have had drug-induced hyperinsulinism.

This child was referred to us after presenting three weeks previously with a single episode of profound hypoglycaemic coma. Unequivocal evidence of hyperinsulinism was found by demonstrating elevated plasma insulin values (36—38 mU/l) for blood glucose (1.0 mmol/l) and absence of ketosis. However, after transfer she was found to have normal starvation tolerance with the appearance of ketosis, normal glucose requirement and glucose tolerance. A calcium infusion failed to induce hypoglycaemia or increase plasma insulin levels, whilst administration of fish insulin showed normal suppression of endogenous insulin secretion (Fig. 2). Armed with this information, it soon became apparent that the child had almost certainly suffered non-accidental administration of an oral sulphonylurea preparation used to treat the maternal diabetes.

The importance of considering non-accidental poisoning in children with hyperinsulinism is further emphasised by Case 17, a 14 months old child suffering recurrent hypoglycaemic seizures due to hyperinsulinism which occurred even in hospital. In between attacks, however, the child had normal starvation and glucose tolerance and normal glucose requirement. The clue to the underlying problem was the temporal relationship of the seizures to feeding and fasting, in that

they always occurred in the early evening and never after overnight starvation. Toxicological screen in blood and urine at these times demonstrated high concentrations of glibenclamide, a drug used in treating the paternal diabetes. Without recognition of "Münchhausen Syndrome by Proxy" [31] it is possible that both of these children could have been subjected to partial or even total pancreatectomy.

With reference to therapy, diazoxide has been used widely during the last 20 years in the treatment of hyperinsulinism with variable and mainly disappointing results [8, 19, 20]. The unpredictability of this treatment is further emphasised in the present study in which all the cases of both nesidioblastosis and insulinoma have benefited from diazoxide therapy only in the short term if at all. Nonetheless, it remains at present the mainstay of medical treatment, other substances including hydrocortisone, phenytoin, propranolol, somatostatin and streptozotocin being either ineffective or associated with important side effects [3].

It is noteworthy that the hyperinsulinaemic hypoglycaemia was a temporary phenomenon in four of our 18 cases. The aetiology of this transient hyperinsulinism is not known. We are aware of only one previous report [29] where spontaneous remission of hypoglycaemia occurred at 4 months of age in one patient with neonatal hyperinsulinaemic hypoglycaemia. These experiences suggest that some children have a temporary regulatory defect of basal insulin secretion. That this can occur, should lead to caution in embarking upon aggressive surgical treatment. Nonetheless, the decision to do so should not be delayed in infants dependent upon massive infusion rates of glucose who do not respond to diazoxide, particularly since surgical resection of an adenoma may be curative. Unfortunately, we know of no endocrine or metabolic marker which would at present identify the nature of the underlying disturbance.

We conclude from this analysis of 18 cases that it is possible to define a practical approach to diagnosis and management of hyperinsulinaemic hypoglycaemia in the paediatric age group. The condition carries serious implications if unrecognised, or when the diagnosis and introduction of effective treatment are delayed. On the other hand, however, the outlook is excellent if the condition is promptly and appropriately treated.

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