Long term follow up of persistent hyperinsulinaemic hypoglycaemia of infancy

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Abstract

Twenty six children with hypoglycaemia were diagnosed and followed between 1975 and 1995. Diagnosis was confirmed by a high insulin:glucose ratio, and low free fatty acid and 3-hydroxybutyrate on fasting. All patients were treated with diazoxide at a maximum dose of 20 mg/kg/day. Requirement of a higher dose was considered as a failure of medical treatment and an indication for surgery. Sixteen children responded to diazoxide; 10 failed to respond and underwent pancreatic resection. Six of the latter group started with symptoms in the neonatal period. Eleven of the 26 children have neurological sequelae. Head growth and neurological outcome correlated well. Additionally, non-specific electroencephalogram abnormalities (slow waves) appear to be indicative of subclinical hypoglycaemia during follow up.

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Hypoglycaemia in the newborn and during the first year of life from whatever cause usually responds rapidly to intravenous glucose.[1] Nevertheless, there is a small group of patients with hyperinsulinism, who experience severe hypoglycaemia and who are difficult to treat. Outcome may be suboptimal in these patients, especially if the diagnosis is delayed or treatment unsuccessful. These patients have been characterised as having "persistent hyperinsulinaemic hypoglycaemia of infancy" (PHHI).[2] The histological basis of the disease has been defined as "nesidioblastosis", "diffuse cell hyperplasia", or "islet cells dysmaturation syndrome".[3–6]

The diagnosis of PHHI is usually made following recurrent hypoglycaemic episodes that occur after a short period of fasting in a child who otherwise appears normal. A low blood sugar associated with inappropriately high insulin (high insulin:glucose ratio), and/or C-peptide, and low free fatty acids and 3-hydroxybutyrate concentrations confirms the diagnosis. The requirement of a high glucose infusion rate to control hypoglycaemia is also characteristic.[2 7]

The cause of PHHI is unknown. Some patients with a familial form of the disease have abnormalities in the sulfonylurea receptor gene.[8] In others it has been postulated that they have a disturbance in the endocrine proliferation of fetal pancreas[6] or an alteration in insulin secretion.[9]

Initial treatment is with glucose and sometimes with steroids; long term hypoglycaemic control involves frequent feeding, controlled protein intake, diazoxide, and/or somatostatin. Several published series of patients with PHHI, treated long term with diazoxide or octreotide, have emphasised how difficult it is to obtain a normal outcome.[10–12] Some patients with poor response to medical treatment require surgery (near total pancreatectomy).

There is limited information available on long term outcome of patients with PHHI. We report our experience of long term care of 26 children with PHHI treated with diazoxide alone, or diazoxide followed by surgery.

Patients and methods

We investigated 26 patients (16 boys, 10 girls) with PHHI diagnosed between 1975 and 1995. Twenty two were born with normal weight for gestasional age and four weighed more than 4000 g (table 1). There was no family history of hypoglycaemia among 41 siblings, including one non-identical twin girl. Hypoglycaemia was first documented during the first week of life in nine patients, and between 30 and 386 days in 17 patients. In the former, PHHI was confirmed at a mean (SD) age of 41 (33) days. The latter were diagnosed between 3 months and 5 years of age (table 1).

All underwent a fasting tolerance test which was discontinued when the patient became symptomatic and/or had a blood sugar concentration of 2.2 mmol/l or below. At the end of the fast, blood was obtained to measure insulin, glucose, C-peptide, free fatty acid and 3-hydroxybutyrate. The insulin:glucose ratio was calculated as pmol/l insulin:mmol/l glucose. A ratio less than 40 was considered normal and more than 100 was considered diagnostic of hyperinsulinism. Values between 40 and 100 were considered suggestive of PHHI. All patients underwent regular clinical review and measurement of insulin:glucose ratio and, when possible, free fatty acids and 3-hydroxybutyrate.

Normal values for glucose and insulin were obtained from 30 normal infants (16 boys, 14 girls) after an overnight fast.

Blood glucose was measured by glucose oxidase, insulin by radioimmunoassay with the charcoal dextran technique,[13] and C-peptide by radioimmunoassay as described by Heding.[14] C-peptide standard and antiserum was a gift from Dr H Frank from Eli Lilly Co (Indianapolis, USA). Free fatty acids were determined with a modified Ducombe technique,[15] and

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Table 1 Clinical data

Patient	*Birth-weight (g)*	*Sex*	*Age of documented hypoglycaemia (days)*	*Age when PHHI diagnosed (days)*	*Diazoxide (mg/kg/day)*	*Prednisone*	*Somatostatin*	*Octeotride*	*Treatment with diazoxide*	*Pancreat-ectomy*	*Age treatment discontinued**	*SDS of height**	*SDS of weight**	*Sequelae*
1	4300	M	1	120	16	Yes	No	No	7 y 10 m	–	–	−0.69	−0.81	SZ
2	3500	F	1	26	20	Yes	No	No	18 m	No	1 y 8 m	1.11	1.44	None
3	2800	M	1	45	20	Yes	No	No	2 m	95%		−0.06	0.85	SZ
										100%	5 m			
4	3300	M	1	14	12	No	Yes	No	1 m	95%	2 m	0.14	−0.17	None
5	4100	F	4	35	20	Yes	Yes	No	2 m	70%		−0.27	−0.21	SZ
					20	Yes	Yes	No	3 m	95%				ST
										100%	6 m			IDDM
6	4800	M	2	53	20	No	No	No	3 m	95%	5 m	−0.23	−0.82	None
7	4000	F	1	44	25	Yes	No	No	4 m	95%	5 m	1.7	0.2	BD
8	3300	M	3	10	7.5	No	No	No	4 m	No	4 m	−0.08	−0.39	None
9	3900	M	1	20	20	No	Yes	No	1 m†	95%		−0.69	−0.21	None
10	2700	M	150	300	15	Yes	No	No	16 y 6 m	95%	19 y	1.31	0.45	SMD-ST
11	3700	M	60	90	15	Yes	No	No	15 y 9 m	95%	16 y	0.58	0.07	SMD
12	3200	F	365	2400	10	No	No	No	8 y 2 m	No	14 y 9m	0.08	0.36	None
13	3400	M	302	366	7	Yes	No	No	7 y	No	9 y	0.73	0.31	None
14	3100	F	334	448	12	Yes	No	No	9 y 3 m	No	10 y 6 m	−0.52	0.21	None
15	3800	M	80	107	12	Yes	No	No	1 y 5 m	95%	1 y 5 m	1.62	1.32	BD
16	3900	M	63	155	10	Yes	No	No	3 y 7 m	No	4 y	0.23	−0.12	None
17	3500	M	147	178	14	Yes	No	No	13 y 6 m†	No		−1.59	−0.67	None
18	3800	F	135	428	12	No	No	No	13 y†	No		0.43	0.54	SZ
19	3400	M	150	216	12	Yes	No	No	2 y 7 m	–	–	0.17	−0.23	None
20	3200	F	330	330	19	No	No	No	4 y 3 m	–	–	−1.58	−1.76	BD
21	2500	F	120	150	10	No	No	No	7 y†	No		0.79	0.22	None
22	4400	F	120	189	12	No	No	No	2 y	No	2 y 6 m	−0.16	−0.69	None
23	3100	F	210	273	11	No	No	No	7 y 5 m†	No		−0.1	−0.17	None
24	4000	M	163	337	10	Yes	No	No	6 y 11 m†	No		−0.81	−0.64	None
25	2800	M	386	410	11	No	No	No	7 y 8 m†	No		−2.24	−2.06	None
26	3100	M	90	120	10	No	No	Yes	10 m	95%	1 y 7 m	−1.01	−1.11	BD

*When hypoglycaemia resolved; †continues with diazoxide; —lost to follow up.
SMD, slight motor disability; SZ, seizures; BD, brain damage (diffuse cortical atrophy with enlarged ventricular system); ST, steatorrhoea; IDDM, insulin dependent diabetes mellitus.

3-hydroxybutyrate was determined with an enzymatic procedure.[16] Values for free fatty acids and 3-hydroxybutyrate obtained during the fasting test were compared to those reported by Bonefont and colleagues.[17]

Follow up assessments included growth, intellectual performance (using the Briac, Termen, Gesell and WISC (Weschler infantile scale coefficient) test), school performance, and metabolic status with an overnight fasting test. Head circumference was followed with the Nellhaus chart. An electroencephalogram (EEG) was performed annually or when requested by a paediatric neurologist.

Student's *t* test for paired samples was used for statistical comparisons.

Results

The insulin:glucose ratio was high during fasting and was also high when C-peptide was converted to equivalent insulin. Free fatty acids and 3-hydroxybutyrate values were low in relation to glucose level and were also low for a normal population of identical age and fasting. Laboratory results obtained during the fasting test are shown in table 2 and the insulin:glucose ratio in fig 1.

In one child (patient 18) the insulin:glucose ratio was less than 40 because the fasting test was performed while the patient was already on treatment with diazoxide. This patient had been referred from another hospital with documented hypoglycaemia requiring a high rate of glucose infusion, typical of PHHI.

All patients began diazoxide treatment as soon as the diagnosis was established. Fourteen

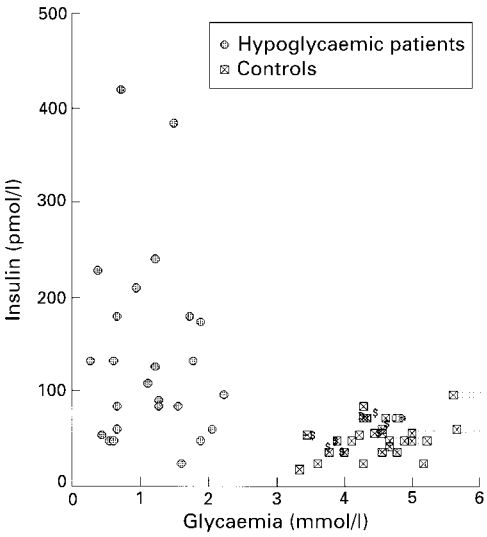

Figure 1 Comparison of hyperinsulinaemic hypoglycaemia with normal controls. Insulin v glucose after variable fasting in hyperinsulinaemic and normal children.

Table 2 Results of the fasting test in hypoglycaemic children before treatment

	Glucose (mmol/l)	*Insulin (pmol/l)*	*C-peptide (pmol/l)*	*Free fatty acids (mmol/l)*	*3-OH-butyrate (mmol/l)*	*Insulin/glucose*	**C-peptide/glucose*	*Fasting (hours)*
Mean	1.16	132.6	68.8	0.36	0.07	159.13	252.4	7.1
SD	0.57	100.2	75.6	0.23	0.04	163.9	292.8	5.1
n	26	26	5	12	12	26	5	26

Insulin/glucose in normal controls is 11.45 (3.89).
*Insulin equivalent.

patients had already received steroids. Somatostatin or octreotide were used in patients who did not respond to diazoxide and before surgery (table 1). Diazoxide was increased from 5–10 mg/kg/day until a normal fasting glucose was reached with normal insulin:glucose ratio, or a maximum dose was reached of 20 mg/kg/day. In one patient (patient 7) a dose of 25 mg/kg/day was used, but was lowered due to encephalopathy with hypertension. The maximum dose of diazoxide used for each patient is shown in table 1.

Diazoxide controlled hypoglycaemia in 16 patients (table 1). Seven discontinued diazoxide after four years six months (range four months to nine years three months) and are asymptomatic; six patients are continuing treatment (average nine years three months) and the remaining three patients were lost to follow up after four years 10 months of treatment (range two years seven months to seven years 10 months). Of the 16 patients who responded to diazoxide, only three had hypoglycaemia during the first week of life (table 1). In two (patients 2 and 8) diazoxide was successfully withdrawn at the age of 18 months and four months, respectively. The other patient (patient 1) was lost to follow up after seven years 10 months of treatment.

Ten patients failed to respond to diazoxide and underwent surgery. Six had their first hypoglycaemic episode during the first week of life. Ninety five per cent pancreatectomy was sufficient to control the hypoglycaemia in seven of the 10 patients. One patient (patient 9) continues to need diazoxide (10 mg/kg/day) after surgery. In the remaining two patients hypoglycaemic episodes continued after surgery, could not be controlled with diazoxide and required permanent somatostatin infusion. Eventually total pancreatectomy was performed in both.

During follow up, some patients had nonspecific changes in a previously normal EEG (slow waves), despite being asymptomatic and having normal blood sugar concentrations. We considered this represented suboptimal control; therefore, we re-evaluated these children with a repeat fasting tolerance test. Results were abnormal in four patients and their dose of diazoxide was increased. Metabolic control improved and the EEG became normal in two patients. The remaining two patients had an unusual outcome. Patient 10 was successfully maintained on diazoxide until the age of 11 years 6 months, when treatment was discontinued by his parents. He remained asymptomatic. At 14 years old an EEG showed slow waves and a repeat fasting test showed hyperinsulinism. He was restarted on diazoxide; EEG abnormalities persisted and he was operated on at 19 years old (fig 2). Patient 11 also responded initially to diazoxide. However, he needed steadily higher doses to control his hypoglycaemia and had slow waves on the EEG. He was operated on at 16 years old. In both patients the EEG became normal after surgery.

Ten patients had various neurological abnormalities (table 1) and/or low intelligence quotient (IQ). Four had an IQ less than 60.

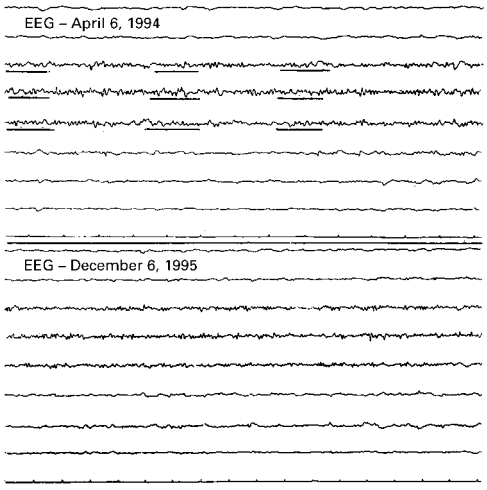

Figure 2 EEG in patient 10 before and after pancreatectomy.

One of these patients also has Turner's syndrome with 46 X ring chromosome. Of the 10 patients with neurological impairment, seven were in the group that required surgical treatment (table 1).

Patients without neurological impairment who were treated for at least three years showed a significant improvement in their head circumference, from −0.4 to +0.6 standard deviation score (SDS) ($p < 0.01$, $n = 12$). In contrast, head circumference after three years of treatment was −1.0 to −0.8 SDS (not significant, $n = 7$) in those patients who developed neurological damage such as brain atrophy on computed tomography or sequelae such as seizures, motor disabilities, and delayed maturation.

Immunohistochemistry of the pancreas in all patients who underwent surgical treatment revealed β cell hyperplasia with an increased number and irregular distribution of islets, with endocrine cells between exocrine acini or in close contact with exocrine ducts. Hyperchromasia and/or nuclear gigantism were also present. We found no adenomas. The pathological abnormalities were similar in all patients, differing only in distribution or degree. No differences were found between those operated on as newborns or adolescents.

Discussion

All the children studied were sporadic cases with no family history of hypoglycaemia. As with other series there was no sex bias.[18]

We established diagnoses by the clinical picture and high insulin:glucose ratio. Hyperinsulinism should not be ruled out even in patients showing insulin:glucose values less than 40 if the clinical picture suggests this disorder. Hyperinsulinism also inhibits the normal response to hypoglycaemia,[19] preventing the increase of free fatty acids and 3-hydroxybutyrate. Therefore, low free fatty acids and 3-hydroxybutyrate values associated with an abnormal insulin:glucose ratio in a child with hypoglycaemia reinforces the diagnosis of hyperinsulinism. Serum C-peptide concentration, which represents total endog-

enous insulin secretion, is also a useful tool in diagnosing hyperinsulinism and complements venous insulin concentration, which represents the amount of insulin available after tissue extraction.[20]

The description of familial forms of hyperinsulinism suggests an autosomal dominant or recessively inherited basis,[21] while sporadic cases show a low prevalence of the sulfonylurea receptor gene.[22]

Patients differ in age of onset and severity of symptoms and response to diazoxide. Children with neonatal hypoglycaemia appear to have more severe disease than those of late onset. They respond poorly to diazoxide and have a higher rate of neurological sequelae. Nevertheless, there are exceptions. Patient 8 developed hypoglycaemia a few hours after birth and was successfully treated with diazoxide, which was withdrawn four months later without further hypoglycaemia. Landau *et al* described a similar patient who developed hypoglycemia on the second day of life with remission after four months.[23] These patients might have "transient" hyperinsulinaemic hypoglycaemia of infancy as defined by Aynsley-Green.[24]

Some of our patients who responded well to diazoxide nevertheless developed neurological impairment. We attribute this outcome in three patients as due to poor treatment compliance. We attributed poor outcome in the remainder to delayed diagnosis and treatment. Our results emphasise the importance of considering whether families will comply with medical treatment when deciding on indications for surgery.

Many of our patients have been on treatment with diazoxide for many years (up to 17 years). Common side effects have been hypertrichosis and poor appetite. Only one patient became hypertensive with a dose higher than 20 mg/kg/day and we did not find haematological abnormalities or decreased serum immunoglobulins. Patients in remission after diazoxide treatment have had a normal outcome; none have developed diabetes or transient hyperglycaemia during follow up.

It has been suggested that children with PHHI may experience asymptomatic hypoglycaemia.[25] These patients, who have normal blood sugar levels when studied, might present with subtle symptoms of hypoglycaemia such as learning difficulties, or non-specific signs of central nervous system involvement such as slow waves in the EEG. Although ATP concentrations significantly decrease only in extreme hypoglycaemia,[26] glucose values below 2.8 mmol/l induce changes in evoked potentials,[27] and in experimental studies blood glucose values below 2.2 mmol/l produce EEG changes, starting with slow waves.[28] According to this concept, the EEG patterns with slow waves found in our patients may be a sign of subclinical hypoglycaemia. The abnormal results of the fasting tolerance tests found in four of these patients, and the EEG improvement in two of them after increasing the dose of diazoxide, highlights the importance of these "subtle" signs of hypoglycaemia.

Head circumference appears to correlate with neurological outcome of treated children. We found statistically significant increments in head circumference in those patients with good neurological outcome. Similar results were found by Landau and colleagues,[23] and Gottschalk and colleagues.[29] In contrast, children with neurological abnormalities showed poorer growth in head circumference. The abnormal head growth seen in these patients could be caused by a decrease in protein synthesis,[30] or by the release of neurotransmitters (such as glutamate or aspartate), and neuronal death during prolonged hypoglycaemia.[31]

We conclude that children with PHHI vary in clinical presentation and outcome. In those patients with neonatal onset the disease is usually more severe, so early surgery should be considered. Treatment with diazoxide at a dose less than 20 mg/kg/day appears to be safe, even when used for a long period. Follow up of these patients should include seeking "subtle" indicators of suboptimal control, such as EEG abnormalities, in order to prevent any further neurological dysfunction and/or damage.

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