PERSISTENT HYPERINSULINAEMIC HYPOGLYCAEMIA OF INFANCY: CASE REPORT

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SUMMARY

Hyperinsulinism, although rare, is the most common cause of persistent hyperinsulinaemic hypoglycaemia in infancy. Because of persistent hypoglycaemia, serious difficulties are encountered in the long term management of this condition. A male neonate, after an uncomplicated full-term pregnancy, had been admitted to another hospital with convulsions on the third post-natal day. Meningitis had been suspected at that time and treated with phenobarbital and he had been discharged from the hospital. At three-months old he was referred to our department for persistent convulsions and lethargy. His parents were of 1st degree consanguinity. His blood glucose level was found to be 24 mg/dl (1.33 mmol/L). Because of the dangerously high insulin level during hypoglycaemia (insulin/glucose >0.3), the absence of ketonuria, and the need for a high dose of glucose infusion (> 15 mg/kg/min) to achieve normoglycaemia and a glycaemic response to glucagon despite the hypoglycaemia, a diagnosis of persistent hyperinsulinaemic hypoglycaemia of infancy was made. Since maximal doses of prednisone, glucagon, diazoxide, octreotide and high infusion of glucose were ineffective in achieving normoglycaemia, a subtotal (80%) pancreatectomy was done. Postoperatively intermittent hypoglycaemic episodes continued. These were controlled with low doses of octreotide. Histology revealed diffuse adenomatous hyperplasia (nesidioblastosis). The boy is now in the sixth post-operative month and developing normally.

INTRODUCTION

Hypoglycaemia is the most common metabolic problem in childhood and, when severe or recurrent, devastating neurological sequelae may occur (1). Severe consequences of hypoglycaemia are seen when the cause is hyperinsulinism. Hyperinsulinism accounts for approximately 1% of all cases with hypoglycaemia(2), but it is the most common cause of persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI). PHHI is also called by other names such as islet cell dysmaturation or dysplasia syndrome, congenital hyperinsulinism, and, previously nesidioblastosis(3). The incidence is reported to be 1 in 50,000 live births(4). Although most cases are sporadic, it is now well recognised that the disorder may be familiar(5). Advances in the molecular genetics of PHHI have revealed abnormalities of sulphonylurea receptor (SUR) gene located on the short arm of chromosome 11; this may explain insulin hypersecretion in such familial cases(6,7). The absence of functional K⁺ ATP channels has recently been shown to induce insulin hypersecretion in sporadic PHHI(8).

The aim of therapy is to maintain euglycaemia to protect the developing brain from possible damage. Diazoxide, somatostatin or a long-acting analog and glucagon, each alone or in various combinations, have been used with varying degrees of success(3,7,9,10). Many children require surgery early in life in the form of a sub-total or total pancreatectomy if medical treatment fails to maintain euglycaemia(9). The results of surgery vary according to the extent of the pancreatic resection(9).

We report the case of a three-month old infant with PHHI who underwent a sub-total pancreatectomy after failing to respond to currently available medical treatments.

CASE REPORT

A male neonate, delivered full term with a birth weight of 4000 gram and following an uncomplicated pregnancy, had been admitted with convulsions to another hospital in the 3rd post-natal day. Meningitis had been suspected at that time and treatment, including phenobarbital for his convulsions, had been begun. He was referred to our department at three months of age because of ongoing seizures and lethargy. He was hospitalised to determine the causes of his condition and his blood glucose level was found to be 24mg/dl (1.33 mmol/L).
The patient is the third child of first degree consanguineous parents. His height was in the 50-75th percentile, his weight was in the 75-90th percentile and his head circumference was in the 10th percentile. Except for mild hepatomegaly, the physical examination was normal. Biochemical data is shown in Tables 1 and 2. Observing the inappropriate insulin increase during hypoglycaemia, the absence of ketonuria, and an exaggerated response to glucagon test eliminated the causes of hypoglycaemia, and, thus, the diagnosis of hyperinsulinism, was confirmed. A pancreatic sonography (US) and the magnetic resonance imaging (MRI) were normal.

Table 1

<table>
<thead>
<tr>
<th>Laboratory characteristics of the patient</th>
<th>Case</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L) (*)</td>
<td>1.8-1.6</td>
<td>&gt;2.8</td>
</tr>
<tr>
<td>Insulin (mU/L) (*)</td>
<td>16-29</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Insulin/Glucose (mg/dl) (*)</td>
<td>0.5-1</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Blood Ph</td>
<td>7.4</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>Lactate (mmol/L) (*)</td>
<td>2.0</td>
<td>0.7-2.1</td>
</tr>
<tr>
<td>Ammoniia (μmol/L)</td>
<td>36</td>
<td>21-50</td>
</tr>
<tr>
<td>Growth hormone (μg/L) (*)</td>
<td>17</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Cortisol (μg/dL) (*)</td>
<td>18</td>
<td>5-24</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>45</td>
<td>10-100</td>
</tr>
<tr>
<td>Triglycerides (μg/L)</td>
<td>0.81</td>
<td>0.30-0.86</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4</td>
<td>1.17-4.70</td>
</tr>
<tr>
<td>Urinary amino acids</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Urinary ketone (*)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

(*) Samples obtained during the acute hypoglycaemic episode.

Table 2

<table>
<thead>
<tr>
<th>Results of the glucagon test</th>
<th>Glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.28</td>
</tr>
<tr>
<td>30</td>
<td>6.27</td>
</tr>
<tr>
<td>60</td>
<td>7.38</td>
</tr>
</tbody>
</table>

He failed to respond to serial changes in medical treatment as follows: Glucose infusions of >15mg kg/min given over a period of seven days, prednisone at 2mg/kg/ day for 10 days, diazoxide, at 12 mg/kg/day as starting and 20 mg/kg/day as maximum dose for 28 days, subcutaneous infusion of octreotide at 10 μg/kg/day as starting and 20 μg/ kg/day as maximum doses for 10 days, a combination of octreotide at 20 μg/kg/day and glucagon at 100μg/kg/day for six days. At this stage subtotal pancreatectomy (80%) was performed. This also failed to achieve normoglycaemia. But addition of octreotide initially at 5 μg/kg/day and later at 2 μg/kg/day achieved normoglycaemia. The histopathological diagnosis of diffuse adenomatous hyperplasia (oestiodoblastosis) was made (Figures 1, 2).

![Figure 1](obvious_nuclear_hyperplasia_and_polymorphism_in_endocrine_pancreatic_islets_FAS_X_400.png)

Endocrine pancreatic islets with obvious nuclear hyperplasia in pancreas separated with connective tissue bands. HE X 200

![Figure 2](it_is_now_his_sixth_post_operative_month_and_he_is_developing_normally_his_height_is_in_the_25_50th_percentile_his_weight_is_in_the_50_75th_percentile_and_his_head_circumference_is_in_the_tenth_percentile.png)

It is now his sixth post-operative month and he is developing normally. His height is in the 25-50th percentile, his weight is in the 50-75th percentile and his head circumference in the tenth percentile.

**DISCUSSION**

PHHI is one of the most difficult metabolic problems in paediatrics. The criteria to diagnose hyperinsulinism include the presence of low plasma free fatty acids and ketone bodies, simultaneous inappropriate plasma insulin release during hypoglycaemia, a glycaemic response to glucagon, despite hypoglycaemia, and the need for a glucose infusion above 10-15 mg/kg/min to achieve normoglycaemia (11). Excess insulin increases the hepatic glycogen synthesis, which is probably one of the factors responsible for hepatomegaly. Some infants have high birth weights due to the anabolic effects of insulin; the weights and heights of these children are generally greater than those of normal children (12). Our patient was large for gestational age, had hepatomegaly and biochemical data that confirm PHHI. In addition, he failed to respond to high dose glucose infusion.
Two forms of PHHI have been reported (13). One is characterised by focal pancreatic adenomatous hyperplasia (focal PHHI) and the other is characterised by a diffuse β-cell abnormality (diffuse PHHI). Whilst diffuse involvement of the pancreas is more common in infancy, localised lesions are seen with more frequency in older children (9). The US, computed tomography and MRI are helpful in diagnosing adenoma if it is echogenic. The pancreatic US and MRI of our patient revealed normal findings.

Diazoxide mobilises glucagon, stimulates catecholamine secretion, and directly inhibits insulin release by inhibiting SUR (3, 7, 9). It is usually ineffective in cases with recessively inherited hyperinsulinaemia, because the mechanism of diazoxide action requires a normal SUR (7). Normoglycaemia, could not be restored in our case, although diazoxide was increased to its recommended highest dose. Because our patient was the child of 1st degree consanguineous parents and there was no response to diazoxide treatment, it is likely that our case presents an autosomal recessive pattern of inheritance of hyperinsulinaemia. Unfortunately, we did not have the opportunity to perform molecular genetic studies at our hospital.

Glucagon and somatostatin produce a prompt and significant increament in glycaemia in cases with PHHI (3). Somatostatin suppresses insulin secretion further downstream at the level of calcium-mediated insulin release (7). A review of all the reported cases suggested that only one fourth to one third were successfully treated with octreotide (3). Despite the use of octreotide with increasing doses, and later together with glucagon, normoglycaemia could not be achieved in our patient. No side effects due to octreotide were observed.

Hypoglycaemia in cases with PHHI may result in brain damage, especially during episodes of stress or recurrent infection (9). Thomas et al. found at least 50% of infants undergoing pancreatic resection were mentally retarded at the time of surgery (2). The time interval between the onset of symptoms and the operation was 5.5±1.53 months in developmentally normal children when compared with 9.6±2.6 months in those mentally retarded (2). For this reason, in patients in whom normoglycaemia cannot be maintained, despite optimal medical treatment, surgical resection should be performed early, and not as a last resort (9). Because our patient did not respond to medical treatment, he underwent a surgical resection at the age of six months.

A surgical resection involves a subtotal pancreatectomy in most patients. Martin et al. (14) reviewed the results according to the extent of pancreatic resection in 81 patients. Of the 118 cases that underwent subtotal (<80%) resection, 45% required additional treatment and 26% needed another operation for persistent hypoglycaemia. Out of the 63 patients having near total (>80%) pancreatectomy, in comparison, only 20% required additional medication and 8% needed another operation. A nearly total pancreatectomy may result in an unacceptably high recurrence risk if not sufficiently complete and, conversely, if too complete, the result is malabsorption and diabetes mellitus (10, 15). Our patient underwent a subtotal (80%) pancreatic resection. As the pancreatic lesion was diffuse and a subtotal pancreatectomy was performed, the postsurgical success to maintain normoglycaemia could not be achieved, which was not an unexpected result. Octreotide 50µg/kg/day was begun and this corrected the patient’s hypoglycaemia. At follow-up, the drug dose was decreased to 2 µg/kg/day. Our patient is now normoglycaemic. Whether or not he will be in need of another operation is a matter of debate at present, and will be clarified at follow-up.

REFERENCES