Persistent neonatal hypoglycaemia due to glucagon deficiency

Glucagon deficiency as a possible cause of persistent neonatal hypoglycaemia has been discussed before (Wagner et al., 1969; Gotlin and Silver, 1970; Zupping er, 1975). Vidnes (1976) recently described a case of persistent hereditary neonatal hypoglycaemia due to glucagon deficiency; therapy with zinc-protamine-glucagon resulted in dramatic improvement. This was the first case in a child where glucagon deficiency was verified by glucagon determination. We here describe a further case of a newborn infant with persistent neonatal hypoglycaemia due to glucagon deficiency and treated by zinc-protamine-glucagon.

Case report

A boy was born after a normal pregnancy in August 1975 as the third child of healthy unrelated parents. He has 2 healthy siblings. No family history of infant deaths from hypoglycaemia was known. Birthweight was 3.7 kg. The child was breast fed, and the first day passed uneventfully. In the evening of the second day he became drowsy and failed to suck. Next morning he was apathetic, breathed irregularly, and rolled his eyes. At admission to a local hospital blood glucose was low (0.9 mmol/l; 16 mg/100 ml) with a metabolic acidosis (pH 7.22, base excess -5.5 mmol/l (-5.5 mEq/l)). Treatment was started with infusion of glucose 10%; after 2 and 4 hours respectively the blood glucose value was 1.6 and 0.5 mmol/l (28-8, 9 mg/100 ml). Apart from the infusion therapy, which was continued, he received feeds of humanised milk, and prednisone was started. The first day after admission several convulsions were noted, but within a few days the clinical condition improved. During the next few weeks several attempts were made to reduce the frequency of oral feedings below 8 times per day, but each time the blood glucose level decreased and his condition deteriorated.

At the age of 3 weeks he was referred to the University Hospital. We found an alert but sweaty and restless baby with a length of 56.5 cm and a weight of 4250 g. The liver was palpable 1 cm below the costal margin. Blood was analysed for cortisol, insulin, thyroxine, growth hormone, lactate, pyruvate, and alanine levels. After 2 hours of fasting the levels of β-hydroxybutyrate and acetoacetate were respectively 37 and 15 μmol/l (0.39, 0.15 mg/100 ml). Reducing substances in the urine were absent. Vanillylmandelic acid excretion was 4.5 mmol in 24 hours. No abnormal organic acids in the urine were detected by gas chromatography. Under a regimen of 12 oral feeds of humanised milk per day, blood glucose varied between 1.8 and 3.0 mmol/l (32, 54 mg/100 ml). A glucagon tolerance test showed a high peak value after 45 minutes and rapid decrease to values below normal. Insulin regulation during the test was normal (Zupping er, 1975; Fig. 1). A glucagon tolerance test showed a normal glucose mobilisation, followed by rapid decrease to values below normal: again insulin regulation was intact (Zupping er, 1975; Fig. 2).

In the light of a possible glucagon deficiency we started treatment with zinc-protamine-glucagon IM at a dose of 2 mg, with 8 feeds per day. For 8-10 hours after the injection the blood glucose level remained above 3 mmol/l (54 mg/100 ml). When given twice daily, the effect lasted for 24 hours.

The clinical condition improved, and the frequency of feeds could be lowered to 6 times per day. In the next few months we had to increase the dosage of glucagon gradually, and stable glucose values could then be maintained. With a regimen of 6 feeds per day and two daily doses of 3.5 mg glucagon IM symptomatic hypoglycaemia did not occur. The patient was discharged in December 1975. After some months the parents discontinued the glucagon
glucagon and insulin values were determined on four occasions starting 10 days after glucagon therapy had stopped. Glucagon was estimated by the method of Aguilar-Parada et al. (1969); antibody 30K was used. Insulin values (Table) varied between 6 and 15 μU/ml, while glucagon values were below 10 ng/l.

**Table Glucagon and insulin determinations**

<table>
<thead>
<tr>
<th>Glucagon* (ng/l)</th>
<th>Insulin (μU/ml)</th>
<th>Glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>4 control infants, fasted 4-10 h</td>
<td>105; 155; 145; 145</td>
<td>5; 9; 4.2; 4.6; 4.7</td>
</tr>
</tbody>
</table>

*Precision of the assay ± 5 ng/l.

Conversions: SI to traditional units—Glucose: 1 mmol/l = 18 mg/100 ml.

Glucagon therapy was resumed and feedings reduced to 6 per day. On neurological examination no specific signs were noted, but the level of motor development was only 4 months at the age of 9 months. Electroencephalogram and echoencephalogram were normal. At the age of 16 months motor development was 11 months.

**Discussion**

Persistent neonatal hypoglycaemia is rare and has been classified by Cornblath and Schwartz (1976) into four groups. In the first group the hypoglycaemia is due to hormone deficiency (congenital hypopituitarism, or insufficiency of growth hormone, adrenal hormone, or thyroid hormone); in the second group to hyperinsulinism; in the third group to hereditary defects in carbohydrate metabolism; and in the fourth group to hereditary defects in amino acid metabolism.

The commoner hormone deficiencies were excluded in our patient by the appropriate tests. Hyperinsulinism was absent. Absence of hepatomegaly and the good glucose response to injection of glucose eliminate glycogen storage disease type 1 and glycogen synthetase deficiency as possible causes of the hypoglycaemia. Normal blood lactate levels and normal serum alanine levels argue against deficiency of one of the gluconeogenic key enzymes. Normal blood levels of amino acids and organic acids exclude hereditary defects in amino acid metabolism. The low levels of glucagon in plasma, and the restoration of almost normal blood glucose levels by long-acting glucagon, support a diagnosis of congenital glucagon deficiency.

There have been several reports of α-cell deficiency and neonatal hypoglycaemia but without

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Fig. 1 Glucose tolerance test. See Table for conversion factor for glucose.

Fig. 2 Glucagon tolerance test.

injections, which resulted in a relapse, and therapy was resumed immediately.

In May 1976, he was readmitted for review. Glucagon was stopped and a regimen of 12 feeds per day started. After 5 days a glucose tolerance test showed much the same result as before. Fasting
measurements of plasma glucagon (McQuarrie et al., 1950; Wagner et al., 1969; Gotlin and Silver, 1970). In Vidnes's (1976) case of persistent neonatal hypoglycaemia due to glucagon deficiency, verified by measuring plasma, treatment with zinc-protamine-glucagon was successful: after 2 months the dosage of glucagon had to be gradually increased as in our case, probably because of antibody production.

Neonatal hypoglycaemia due to glucagon deficiency may be extremely dangerous for the neonate. During glucose need it is glucagon, through a mechanism that remains to be elucidated, that converts the liver to a 'ketogenic mode' and thereby maintains a level of hepatic ketone production necessary to meet cerebral fuel needs (Unger and Orci, 1976). The ketones are an important alternate substrate for the neonatal brain. Ketogenesis in our patient was not adequately studied because the fasting period was limited.

Summary

In a newborn baby, suffering from persistent severe hypoglycaemia with convulsions glucagon deficiency was shown. Treatment with zinc-protamine-glucagon injection twice daily resulted in normal blood glucose levels. Motor development is delayed.

We thank Mr J. B. C. van Veen (Novo Industries AS, Amsterdam) for the zinc-protamine-glucagon preparation, and Dr T. J. Benraad (Department of Medical Biology) for insulin and growth hormone measurements.

References


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Pulmonary interstitial emphysema requiring lobectomy

Complication of assisted ventilation

Ventilatory techniques for treating newborn infants with hyaline membrane disease (HMD) have led to improvement in prognosis (Rawlings et al., 1971), although their use involves potential hazards (Reynolds, 1975). We describe an infant with HMD treated with intermittent positive pressure ventilation (IPPV) who developed localised pulmonary interstitial emphysema which progressed to produce tension and to require lobectomy.

Case report

This male infant was the product of the mother's first pregnancy, this being complicated by diabetes. Labour began spontaneously at 36 weeks' gestation and after 11 hours the infant was delivered with the assistance of forceps. Apgar score was 5 at 1 minute and apart from intranasal oxygen, no resuscitation was required. The birthweight was 3040 g and no malformations were detected. Soon after delivery expiratory grunt, tachypnoea, rib retraction, and cyanosis developed, and chest x-ray showed a reticuloalveolar pattern consistent with HMD.

At 3 hours arterial oxygen tension (PAO2) was only 67 mmHg (8.9 kPa) breathing 100% oxygen. Nasal continuous positive airways pressure was begun. At 5 hours, due to continued deterioration, an endotracheal tube was passed and IPPV started, using a Loosco Amsterdam Infant Ventilator. Inspired pressure was 20-25 cm H2O with a positive end expiratory pressure of 5 cm H2O and the inspired oxygen concentration (FIO2) was 1-0. On this regimen the infant improved and FIO2 was gradually reduced to 0-6.
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