Persistent Neonatal Hyperinsulinaemic Hypoglycaemia (Nesidioblastosis) in two Omani Siblings

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Two female siblings, the products of a first cousin marriage presented with severe hypoglycaemia in the early neonatal period. Serum insulin levels were 25.8 mIU/litre and 21.6 mIU/litre respectively. The histology of the pancreatic glands revealed scattered areas of hypertrophied islet cells among normal cell groups with ducttodocrine proliferation thus confirming a diagnosis of nesidioblastosis. This is the first case report of the disorder in Omani children and the family pedigree was in keeping with an autosomal recessive mode of inheritance.

Better obstetric care together with increased awareness of the need to prevent hypoglycaemia by early feeds at birth have decreased the incidence of early ‘transitional’ hypoglycaemia in our nurseries. Although nesidioblastosis (MIM 256450) is a rare disease, yet it is the commonest cause of persistent hypoglycaemia in infants under the age of 1 year. In this disorder, the B-cell functional disturbance leads to the development of hypoglycaemia and inappropriate hyperinsulinism.

Nesidioblastosis may cause unexpected early neonatal death and other siblings may be affected. The occurrence of permanent neurological damage to these infants has been considerably diminished due to an early and aggressive approach to diagnosis and treatment. All the infants with documented nesidioblastosis have had severe intractable hyperinsulinaemic hypoglycaemia requiring partial or total pancreatectomy.

We report two affected siblings who had both manifested severe symptomatic hypoglycaemia in the form of convulsions within the first week of life and who did not respond to medical management and in whom surgery was the only effective treatment.

Case Materials

The patients (Case 1 and Case 2) were female siblings and the products of a first cousin marriage. Both parents were Omani Arabs and healthy. The family pedigree is shown in Fig. 1. There were two abortions and one still birth. The other three siblings were all well.

Case 1

This patient, now a 4½-year-old girl, had had an uneventful normal full term delivery (birth weight 3.7 kg with a length of 52 cm and head circumference 34 cm: all around the 50th centile) was discharged at 48 h but readmitted after 2 days with convulsions and undetectable blood glucose level with the glucose oxidase strip (Dextrostix) method on admission. She responded well to intravenous dextrose 8 mg/kg/min and frequent...
feeds. Investigations at this time showed no evidence of infection. Plasma and urinary amino acids were normal, ultrasound of skull did not detect any abnormality and tests for urinary reducing sugars, glucose and ketones were negative. Blood gases showed oxygen of 71.4 mmHg, carbon dioxide 35.1 mmHg with a base excess of −4.5 and a pH of 7.35. She was discharged at 12 days, asymptomatic but still requiring frequent feeds to keep the plasma glucose constantly above 2.2 mmol/litre.

Further generalized seizures occurred at the age of 4 weeks. The blood glucose dextrostix test was noted to be nil but responded to a bolus dose of 10 ml (25%) dextrose. However, low values of plasma glucose were still present (ranging from 1.3–2.2 mmol/litre) and she was therefore started on intravenous dextrose 11 mg/kg/min and continuous tube feeds. Since the plasma glucose was intermittently low, intravenous hydrocortisone 25 mg/6 hourly was tried as glucagon was not available. The condition temporarily stabilized.

The most likely diagnosis was hyperinsulinism and the baby was thus transferred to the London Hospital for Sick Children where she was further managed. The hydrocortisone dosage was gradually reduced and frequent hourly feeds were started. She again developed hypoglycaemia before a feed was due and the plasma insulin was measured and found to be 25.8 mIU/litre with a corresponding glucose level of 1.1 mmol/litre (see Table 1). Serum ammonia, lactate levels and three hydroxybutyrate concentrations were all within normal limits. The plasma carnitine levels were normal and there were no organic acids in the urine. An EEG showed moderate abnormal discharges around the middle third of the head during sleep.

The above investigations thus confirmed that her hypoglycaemia was due to hyperinsulinism and she was started on diazoxide 10 mg/kg/day, hydrochlorothiazide and potassium chloride. However, despite this and continuous feeds her plasma glucose continued to fall regularly to 2 mmol/litre and so the nasogastric feeds were enriched with 15% carbohydrate and the dose of diazoxide increased to 20 mg/kg/day. Further low blood glucose levels were noted and in one occasion following an enteropathogenic Escherichia coli diarrhoea, she required glucagon 100 μg/kg intramuscularly. In view of the failure of the medical treatment of her hyperinsulinism for approximately
2 weeks, she was referred for subtotal pancreatectomy. There was no adenoma and 95% of the pancreatic tissue was removed. She remained stable during the procedure and was given prophylactic antibodies (ampicillin and gentamicin).

Her postoperative plasma glucose level rose to 22–25 mmol/litre and treatment with soluble insulin infusion was commenced on a sliding scale. At 24 h after operation she had asymptomatic hypoglycaemia and the insulin dose was readjusted. One week after operation she was gradually started on subcutaneous insulin and an exocrine pancreatic supplement (Creon, Duphar-Germany) was added. After 21 months both drugs were successfully discontinued.

However, there are still occasional mild episodes of symptomatic hypoglycaemia in the form of lethargy and twitches which respond well to sweet drinks and frequent snacks. Her overall development is within normal limits for her age.

Case 2

The patient, now a 2½-year-old girl, was born at term by emergency lower segment Caesarean section for fetal distress, weighed 4.18 kg and looked like the baby of a mother with gestational diabetes. The Apgar score was 6 at 1 min and 9 at 5 min. She developed secondary apnoea and was resuscitated with a bag and mask. There was leaking per vagina of amniotic fluid and maternal fever during the last 24 h prior to delivery and so an infection screen was done and the newborn was given crystalline penicillin and gentamicin.

At 13 hours of age she was observed to be jittery and the random plasma glucose level was 1.1 mmol/litre. Thus, her feeds were adjusted to 2 hourly and later 1 hourly intervals. At 18 h she developed generalized seizures and the blood glucose level by Dextrostix 1 h after a feed was unrecordable. Blood plasma glucose levels were still low in spite of a bolus of 8 ml (25%) dextrose intravenously. Therefore, a dextrose infusion at a rate of 11 mg/kg/min was started together with intravenous hydrocortisone at 4 mg/kg/day. Apart from the mild tachypnoea on day 1, physical examination remained within normal limits with normal blood gases and negative glucose and ketones in urine. The blood glucose concentrations still continued fluctuating below normal levels and in view of the history of persistent hypoglycaemia in the previous sibling, the plasma insulin level was measured and found to be 21.6 mIU/litre with a plasma glucose of 1.7 mmol/litre (see Table 1). Oral diazoxide 10 mg/kg/day was then started but blood glucose levels continued to fall in spite of increasing the dose to 15 mg/kg/day in addition to maximal intravenous and oral glucose supplements. The patient did not require chlorothiazide but developed moderate hirsutism. Somatostatin analogue could not be tried due to unavailability of the drug.

After a 1-month trial of only partially effective medical treatment she was referred for surgery. A nearly total pancreatectomy was done preserving a small collar of pancreas around the pancreatic duct/duodenal junction. The surgical specimen revealed a pancreas with histological features of nesidioblastosis. The postoperative period was uneventful. The patient required 6 weeks treatment with insulin injections (1.5 U of Lantard, Novo-England daily) due to hyperglycaemia after the operation. She remained stable with no more convulsions or hypoglycaemic episodes. The insulin injections were eventually discontinued and she remains well.

Discussion

Two female siblings with nesidioblastosis are described whose parents are both well and consanguinous. This is a further confirmation of the autosomal recessive inheritance of this disorder. The first report was of two siblings of different sexes. Other data in the literature confirm reports of familial occurrence although the relative incidence of sporadic cases appear to be high. A study of seven pedigrees and 28 families have provided further evidence for autosomal recessive inheritance.

The condition has several histopathological pictures. The two main forms of nesidioblastosis recognized are focal and diffuse types both of which occur with equal frequency. They can appear in the same pedigree suggesting that these two apparently different histological appearances may be different manifestations of the same basic defect.

In patient 1 the pathology of the pancreatic tissue showed scattered focal groups of islet cell hyperplasia with duct-endocrine proliferation and hypertrophied cells with giant nuclei. In the other sibling there were diffuse lesions with irregular sized islets. A similar picture may be found in normal babies dying from causes unrelated to hypoglycaemia. Immunochemistry showed that they are all related variants of inappropriate pancreatic development during fetal life.

Hyperinsulinism occurring after the first 6 months of life is more likely to be due to a localized form of the disease such as an isolated adenoma. The criteria for diagnosing hyperinsulinism which are high levels of plasma insulin (>10 μU/ml) and hypoglycaemia were clearly fulfilled in our two patients (see Table 1). The elevation in insulin levels may not have been grossly abnormal but were inappropriate for the degree of hypoglycaemia.

The majority of patients with nesidioblastosis present with symptoms of hypoglycaemia, including convulsions during the first few days of life. Both the siblings described here presented with this picture and EEG findings like those from patient 1 may be similarly seen (though they are not specific) following episodes of hypoglycaemia.
The serum lactate and three hydroxybutyrate levels were both compatible with hyperinsulinism.

The medical management of hyperinsulinism includes frequent high caloric feedings and glucose infusions sometimes at a rate as high as 15 to 20 mg/kg/min. These infusion rates are usually insufficient to maintain euglycaemia. Diazoxide in a dose of up to 20 mg/kg/day usually with chlorothiazide has been most commonly used. Prolonged treatment can lead to complications such as heart failure due to water retention; and hirsutism as shown in patient 2. The addition of hydrocortisone has been described not to be of value but there was temporary relief when it was given to both our patients. Glucagon has a transient effect in a dose of 0.1 mg/kg as an emergency treatment, it mobilizes the hepatic glycogen stores but also stimulates insulin secretion. Somatostatin on the other hand can suppress insulin secretion and can be used as a diagnostic test. Somatostatin analogue is longer acting and is given by subcutaneous injections as a short-term management of hyperinsulinism.13

Human growth hormone can be effective in the treatment of hyperinsulinism in neonates and it can be used as short-term management but not in an emergency since the onset of action is 12 h after administration.

Until the long-term effects of somatostatin analogue given for a long period are known the treatment of choice in this rare but devastating disorder remains a near-total pancreatectomy. Subtotal pancreatectomy should be avoided as preservation of excess pancreatic tissue may lead to relapses due to hyperinsulinism later. It is most important that the condition be diagnosed promptly not only for the swift treatment needed but also in order to provide genetic counselling.

References