Lesson of the Week

Neonatal hypoglycaemia: an important early sign of endocrine disorders

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The incidence of hypoglycaemia is greatest in the neonatal period, and the condition is usually associated with "small for dates" infants, although rare causes have been described.¹ Persistent neonatal hypoglycaemia, however, is usually caused by endocrinopathies or disorders of hepatic metabolism.² We present some of our experience of endocrine disease presenting as neonatal hypoglycaemia as this important association is not always appreciated.

Case reports

CASE 1

A 3 year old girl was referred because of persistent early morning convulsions and inadequate growth. She had been born after a full term normal pregnancy and delivery. Birth weight was 4000 g. At 24 hours of age she became floppy with a blood glucose concentration of 0.1 mmol/l (2 mg/100 ml). Despite an intravenous dextrose infusion the blood glucose concentration remained low for three days. During her first year her mother noticed that regular feeding decreased her irritability. Frequent early morning convulsions, described as febrile in the absence of any documented fever, occurred in the first year. Her delayed motor milestones were attributed to treatment with phenobarbitone, which did not have any effect on the recurrence of convulsions.

Intravenous insulin (0.1 U/kg) given at the age of 3 years induced a fall in blood glucose concentration to 0.9 mmol/l (16 mg/100 ml) and a maximum serum growth hormone response of only 2.1 mU/l (normal >20 mU/l). Plasma cortisol concentration, in response to this severe hypoglycaemic stimulus, attained a maximum value of 203 nmol/l (7.4 µg/100 ml) (normal >550 nmol/l (>20 µg/100 ml)). Serum thyroxine concentration was 56 nmol/l (4.4 µg/100 ml) (normal range 60-140 (4.7-10.9)) and associated with an inadequate response of thyroid stimulating hormone to intravenous thyrotrophin releasing hormone. Replacement treatment was begun with thyroxine and hydrocortisone, and no further convulsions occurred. There was an excellent growth response to treatment with human growth hormone (fig 1). High resolution computed tomography showed aplasia of the anterior pituitary (fig 2).

CASE 2

A girl was referred at the age of 2. Pregnancy and maternal glucose tolerance had been normal. Labour had been induced for postmaturity and delivery achieved by caesarean section for failure to progress. Birth weight was 3400 g. On the second day of life unexplained severe hypoglycaemia occurred, which responded to intravenous dextrose and frequent feeds. Throughout the first year she was drowsy if fed less than every two hours, which resulted in enormous emotional and physical demands on her mother. At the age of 21 months she was observed to have developmental delay and

Neonatal hypoglycaemia is a potent cause of neurological damage and may be due to endocrine dysfunction

FIG 1—Growth chart of girl in case 1 compared with normal girls. ■ represents bone age. Start of treatment with human growth hormone shown by vertical arrow.

short stature. After intravenous insulin (0.1 U/kg) had been given for an insulin tolerance test her blood glucose concentration became unrecordable for two hours and no growth hormone was secreted, although there was a normal plasma cortisol response to 810 nmol/l (29.4 µg/100 ml). After these investigations she was referred to this hospital. Daily treatment with growth hormone adequately controlled her hypoglycaemia and resulted in accelerated growth (fig 3). High resolution computed tomography showed pituitary hypoplasia.

At 3 years she lacked energy and had morning drowsiness without hypoglycaemia. Further endocrine assessment showed morning plasma cortisol concentrations below 110 nmol/l (4.0 µg/100 ml). Her symptoms resolved with cortisol replacement treatment. At 5 years she remained ataxic.

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FIG 2—High resolution (GEC 8800) computed tomogram obtained in case 1. Computed reconstruction through midline of anterior and middle fossae in sagittal plane is shown; nasal sinuses can be seen on left. Pituitary fossa (arrowed) is shallow, and a distinct pituitary gland is absent.

FIG 3—Growth chart of girl in case 2 compared with normal girls. ■ represents bone age. Start of treatment with human growth hormone shown by vertical arrow.

CASE 3

A 6 month old boy was referred with convulsions and developmental delay. Pregnancy and delivery had both been normal. Birth weight was 5500 g. A convulsion occurred at 4 days of age, and although the blood glucose concentration was 2.0 mmol/l (36 mg/100 ml), the cerebrospinal fluid glucose concentration was unrecordable. Feeding every three hours did not entirely prevent convulsions, and he was treated with diazepam. At 6 months he had psychomotor delay and spastic quadriplegia. With his normal three hourly feeding regimen a random blood glucose concentration of 0.6 mmol/l (11 mg/100 ml) was associated with an inappropriately high serum insulin concentration of 39 mU/l, indicating hyperinsulinism.³ Nesidioblastosis was shown histologically after a 90% pancreatectomy. This procedure produced satisfactory control of blood glucose concentrations but only after permanent neurological damage had resulted from persistent hypoglycaemia.

Discussion

Hyperinsulinism (case 3) is probably a more common cause of hypoglycaemia in the first year of life³ than isolated growth hormone deficiency (case 2) or multiple pituitary hormone deficiency (case 1).⁴ In none of our patients, however, were these differential

diagnoses considered during the neonatal period. The investigation of neonatal hypoglycaemia and the possible endocrine aetiologies have been described elsewhere.² All three patients had persistent convulsions that continued after the neonatal period and were inappropriately and ineffectively treated with anticonvulsants. Early morning convulsions, the necessity for frequent feeding and the failure of anticonvulsant medication should alert clinicians to the probability of continuing hypoglycaemia.

Permanent neurological handicap may result from a delay in diagnosis (cases 2 and 3), and in our experience it is only when other signs, such as growth failure or developmental delay, develop that investigation is begun. By this time the chance of an early diagnosis has been missed. In children with pituitary disorders clinicians should beware of an evolving endocrinopathy (case 2) that has the potential for further hypoglycaemia.

We recently reported on two other children with endocrine disease who presented later in childhood but who had a clear history of neonatal hypoglycaemia and consequent developmental delay. As in the present cases anticonvulsant drugs were ineffective and prolonged delay occurred before diagnosis. One girl had hypoplastic optic nerves and pituitary dysfunction and presented at age 14 with growth failure, having had persistent early morning convulsions throughout childhood.⁵ A second had had hyperinsulinism from the neonatal period and was treated during her first 16 months for frequent febrile convulsions, although she did not have a fever.⁶

A long term illness entailing frequent convulsions and developmental delay may be a great burden to the parents, which may be increased by the effort of feeding every two hours day and night. Such parents may in our experience falsely seem unreasonable in their demands on the medical profession. Persistent hypoglycaemia has varied symptomatology but a uniform consequence of neurological delay. Hypoglycaemia, even in the neonate, is not a diagnosis but a sign of an underlying disorder; investigation in the neonatal period should enable early and appropriate treatment to prevent permanent neurological sequelae.

References

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Is there any reported evidence that hypokalaemia may result in difficulty in swallowing? Which food stuffs are most rich in potassium?

Progressive hypokalaemia can cause peripheral muscular weakness, predominantly of the legs, with sparing of muscles innervated by the cranial nerves. Difficulty in swallowing, therefore, is not a feature of hypokalaemia, whatever its cause—for example, hyperaldosteronism, familial hypokalaemic periodic paralysis, losses arising from the gastrointestinal tract, drug treatment—for instance, diuretics—or liquorice and its derivatives. If, however, at the same time as losing potassium a person also suffers from a deficiency of magnesium he may have difficulty in swallowing.¹ This will only resolve with magnesium supplementation and not with potassium supplementation alone. Potassium is present in nearly all foods, particularly fresh meat, fish, vegetables, fruit, and fruit juice.—G MACGREGOR, honorary consultant physician, London.

- 1 Flink EG, Stutzman FL, Anderson AR, König T, Fraser R. Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremors. *J Lab Clin Med* 1954;43:169-83.