Hypoglycaemia in Infancy and Childhood*

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Hypoglycaemia is only a symptom of some underlying disease process. Lack of glucose, the essential nutrient of the developing nervous system, may result in permanent alteration of brain structure and function. While to discover the cause of hypoglycaemia sometimes requires careful and sophisticated investigation, in this brief review we shall outline how the commoner causes of hypoglycaemia (blood sugar less than 50 mg/100 ml) in infants and children can be recognized and treated.

Convulsions are the commonest presenting symptom of hypoglycaemia at any age, but particularly under 1 year. Pallor, weakness, profuse perspiration, and limp spells may occur. In older children, weakness, fatigue, headache, drowsiness, and irritability may be present. If such symptoms occur before meals or after prolonged fasting (early morning), hypoglycaemia should be suspected. Small infants eat frequently but still may have hypoglycaemic convulsions.

Physical examination often reveals a few diagnostic clues. Hepatomegaly suggests glycogen disease or Reye's syndrome. Short stature may point to an endocrine cause. A careful neurological and developmental examination is part of any assessment.

Recurrent symptoms associated with the finding of less than normal blood sugar values establishes the diagnosis. However, if the hypoglycaemia is intermittent, the diagnosis is more difficult. In these cases provocative tests of various types are necessary (see below and Table).

The causes of hypoglycaemia in infancy and childhood are best thought of according to the age of onset of symptoms, and the Table lists the commoner causes of hypoglycaemia at different ages, and the procedure most appropriate for confirming the diagnosis. Details of the various provocative tests are beyond the scope of this

review but can be found in the excellent monographs by Cornblath and Schwartz (1966) and Marks and Rose (1965) where a comprehensive list of the causes of hypoglycaemia is to be found.

Clinical Differentiation

In children under 1 year of age, hypoglycaemia, associated with hepatomegaly, is usually due to diseases in the liver. *Glycogen storage disease of the liver* Types 1 (glucose-6-phosphatase), 3 (debrancher), and 6 (phosphorylase), and the glycogen synthetase enzyme defects are associated with hypoglycaemia. Ketonuria, acidosis, hyperuricaemia, hyperlipidaemia, and skin xanthoma suggest *Von Gierke's disease* (Type 1). If glycogen disease of the liver is suspected, various stimulation tests, particularly glucagon or adrenaline in the fed and fasted states, as well as intravenous galactose and glycerol infusions, help to localize the defect (Sidbury, 1969; Senior and Loridan, 1968). Ultimately, a liver biopsy with enzyme assays must be performed.

Reye's syndrome must be considered in a child who, previously well, suddenly develops seizures, hypoglycaemia, and hepatomegaly after a minor infection, usually upper respiratory. Reye's syndrome is lethal in a high percentage of cases but recovery can occur. The liver cells are usually found to be stuffed with fat. The aetiology is not understood, and the cause is unknown but is likely to be multiple, for example toxic, viral, and so forth (Norman, 1968).

Severe gastroenteritis in infants can be associated with profound hypoglycaemia which responds to intravenous glucose and usually does not recur.

Central nervous system disorders can be associated with severe and persistent hypoglycaemia. Which comes first, the central nervous system damage or the hypoglycaemia, is often difficult to establish (Knobloch *et al.*, 1967).

Islet cell tumours of the pancreas are uncommon at any age but are particularly rare in infants. The

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TABLE
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Cause	Most Useful Diagnostic Procedures
<p><1 year of age</p> <p>Glycogen disease of the liver Reye's syndrome (fatty liver, encephalopathy, hypoglycaemia)</p> <p>Gastroenteritis Central nervous system disease Islet cell tumour of pancreas</p> <p>Idiopathic hypoglycaemia of infancy</p>	<p>Glucagon and/or adrenaline stimulation; liver biopsy and enzyme assay</p> <p>Lethal or self-limited; extensive investigation only required if hypoglycaemia persistent and recurrent</p> <p>Self-limited, responds to intravenous glucose</p> <p>History of prenatal or perinatal insult before onset of symptoms</p> <p>Rare under 3 years; blood insulin levels may be normal; pancreatotomy for severe and persistent hypoglycaemia unresponsive to therapy</p> <p>Frequent blood sugars; rule out other disorder by hormone assays; intravenous tolbutamide test in doubtful cases</p>
<p>1-3 years of age</p> <p>Ketotic hypoglycaemia</p> <p>Reyels syndrome Gastroenteritis Hypopituitarism</p> <p>Adrenal insufficiency</p>	<p>Low birthweight for gestational age, neonatal hypoglycaemia, morning seizures with hypoglycaemia and ketonuria; blood sugar response to high fat—low calorie diet</p> <p>See above</p> <p>See above</p> <p>Blood growth hormone, insulin, cortisol, thyroxine, metynapone test, skull x-rays, bone age</p> <p>Blood electrolytes, intravenous ACTH test, blood cortisol levels</p>
<p>>3 years of age</p> <p>Islet cell tumour of pancreas</p> <p>Ketotic hypoglycaemia Hypopituitarism Adrenal insufficiency</p>	<p>Intravenous tolbutamide test with plasma insulin levels; laparotomy may be required in problem cases</p> <p>See above</p> <p>See above</p> <p>See above</p>

hypoglycaemia they produce is difficult to distinguish from severe idiopathic hypoglycaemia except when a pancreatectomy is performed (Grant and Barbor, 1970).

So-called *idiopathic hypoglycaemia of infancy* is the commonest type under the age of 1 year. In children with this condition physical growth is normal and the liver is not enlarged. Blood sugars are usually low after 3 to 4 hours of fasting and sometimes shortly after meals (suggestive of leucine sensitivity). Evidence of mental retardation is variable but may be profound. The severity of the retardation depends on the frequency and duration of symptoms.

In diagnosis, *provocative tests* are usually only necessary where the hypoglycaemia is intermittent. To ensure the patient's safety prolonged fasting before the test should be avoided, and an intravenous infusion should be running so that 50% glucose can be administered at once if hypoglycaemia develops.

Leucine sensitivity occurs in about one-third of children with idiopathic hypoglycaemia (Cochrane, 1960). Leucine sensitivity, and the sustained blood sugar response to intravenous tolbutamide, are manifestations of an exceptional pancreatic response to usual stimuli. Though insulin levels in blood from the pancreatic vein are not available, values in the blood from peripheral veins may be

inappropriately high in many of these children (Ehrlich and Martin, 1967). Values for peripheral venous insulin may be much higher in the child with an islet cell adenoma of the pancreas than in the child with idiopathic hypoglycaemia. Adenoma is so rare at this age that characteristic values are not established and it can only be ruled out with certainty by laparotomy.

In children over 1 year of age, *ketotic hypoglycaemia* is a common cause of hypoglycaemia (Colle and Ulstrom, 1964). The child is likely to have been of low birthweight for gestational age, have had some transient distress in the neonatal period, in some cases due to hypoglycaemia. The child improves and remains symptom free until he is over 1 year of age. Typically he awakes early in the morning, feels unwell, is nauseated, vomits, and then convulses. Hypoglycaemia and ketonuria are found. Intravenous glucose promptly relieves the symptoms and a further hypoglycaemia is difficult to demonstrate. However, a high fat, low calorie diet induces ketonuria in about 11 hours in patients with the condition, as compared with about 22 hours in controls. Hypoglycaemia with symptoms develops within 24 hours of beginning the diet in patients, while controls remain symptom free for the 48-hour period (R. M. Ehrlich, 1969: unpublished data). In ketotic hypoglycaemia, growth hormone, insulin, and cortisol levels in the blood are

normal but urinary adrenaline may be low. Ketotic hypoglycaemia may be confused with epilepsy, if the blood sugar is not measured at the appropriate time. Once the true condition is recognized, seizures can be prevented by frequent feeding.

Occasionally hypoglycaemia is the first feature of *hypopituitarism*, though symptoms and signs of other hormone deficiencies are usually present. In space-occupying suprasellar lesions, signs of increased intracranial pressure, visual field defects and failing vision may also occur. Hypoglycaemia may be the first sign of isolated growth hormone and/or ACTH deficiency.

The hypoglycaemia found with *adrenal insufficiency* (Addison's disease) is usually associated with increased skin pigmentation and electrolyte imbalance from mineralocorticoid deficit.

Islet cell tumours of the pancreas occur at any age, but are unusual under the age of 3 or 4. When hypoglycaemia begins at this age, a diligent search must be made for such a lesion. Blood insulin levels in these cases may be high on fasting or after provocative stimuli (tolbutamide, glucose or leucine), but to demonstrate the increased insulin levels repeated sampling may be necessary. Since not all adenomas are associated with hyperinsulinism, exploratory laparotomy may eventually be required if symptoms are severe and persistent (Salinas *et al.*, 1968).

Finally, some cases of hypoglycaemia defy aetiological classification. This failure reflects the imperfection of techniques for *in vivo* assessment of carbohydrate metabolism, particularly gluconeogenesis in the liver.

Problem Cases

Three groups of children pose special problems for the paediatrician.

(1) The child with symptoms suggestive of hypoglycaemia (episodes of pallor, drowsiness, headache, irritability relieved by food) but in whom blood sugar values are normal.

(2) The child with symptoms appropriate to hypoglycaemia in whom a low blood sugar is found only once.

(3) The *symptom-free* child in whom a low blood sugar (often 40 to 50 mg/100 ml) is found only once.

The child with symptoms suggestive of hypoglycaemia demands a detailed history. Epilepsy, migraine, anxiety, behaviour disorders, pheochromocytoma, may all mimic hypoglycaemia. Functional hypoglycaemia, seen in adults, is rare in children but some do experience lightheadedness, drowsiness, and pallor after meals, particularly if vigorous physical activity has occurred shortly after

eating. Hypoglycaemia can rarely be proven in these children. Their symptoms may be due to a rapid fall in blood sugar with subsequent adrenaline release. If the intravenous tolbutamide test is normal, no further investigation is indicated.

For the child with symptoms of hypoglycaemia and in whom one low blood sugar value has been obtained, complete investigation should be undertaken. After a careful history and physical examination, a 6-hour glucose tolerance test with insulin and growth hormone levels, intravenous tolbutamide test with insulin levels, diurnal blood cortisol levels, and serum electrolyte determinations should be made. The skull should be x-rayed and skeletal maturation estimated. If ketotic hypoglycaemia is suspected, a provocative ketotic diet should be tried before other tests.

The child reported to have had one low blood sugar but no symptoms of hypoglycaemia is a diagnostic challenge. If a careful history and physical examination offer no clue, further investigation beyond repeating the blood sugar determination periodically is unnecessary.

Management

Hypoglycaemia is a medical emergency to be promptly treated with intravenous 50% glucose, 0.5 to 1.0 g/kg body weight by a rapid injection, followed by an infusion of 10% to 20% glucose at a rate sufficient to keep the blood sugar over 50 mg/100 ml. Once the acute emergency has passed, investigation and treatment can begin.

If a specific cause is found, treatment is directed against that cause, for example administration of growth hormone, or cortisone, or surgery.

Children for whom no specific treatment is available, are fed frequently: infants every 4 hours day and night with extra feedings of glucose and water in between, and older children, a bedtime snack and a feeding before the parents retire. If the hypoglycaemia is ketotic, frequent feedings and extra carbohydrate-rich drinks during intercurrent illnesses can prevent seizures in most cases. Since ketonuria precedes hypoglycaemia, testing the urine for ketones will indicate when more vigorous therapy is needed. The prognosis is excellent since these children 'grow out' of their problem.

Idiopathic hypoglycaemia of infancy is difficult to treat. Frequent feedings minimize hypoglycaemic episodes in some children. When hypoglycaemia has been attributed to leucine sensitivity, some investigators report benefit from use of low leucine diets. Prednisone has controlled hypoglycaemic attacks, but the doses required often

produce unwanted side effects, such as a cushingoid appearance and growth retardation.

Diazoxide, 10 to 15 mg/kg per day, in divided doses given every 6 to 8 hours, has proved to be the most useful therapeutic agent (Ehrlich and Martin, 1969). Most children with idiopathic hypoglycaemia respond by an increase in blood sugar and a lowering of plasma insulin levels. At this dose the major side effect seen in 5 patients on long-term therapy (18 months to 4½ years) was hirsutism. Meanwhile linear growth has been normal and no seizures have occurred.

Subtotal pancreatectomy should be carried out if hypoglycaemia is not controlled by diet, prednisone, diazoxide, or a combination of these. The operation will either effect a cure or make management easier (R. M. Ehrlich, 1966, unpublished data).

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