Ketotic hypoglycaemia of childhood

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Summary

A patient with recurrent convulsions in childhood and associated ketotic hypoglycaemia is described. Hypoglycaemic attacks started at the age of 3 years and 4 months and continued until 9. At present (aged 15) the patient is mentally retarded, has epilepsy, high tone deafness and a major behaviour disturbance. Prednisone therapy failed to prevent hypoglycaemic convulsions and eventually irreversible brain damage. Intramuscular glucagon and adrenaline were ineffective in raising the blood glucose during acute hypoglycaemic attacks.

Investigations at 3 years and 7 months and at 14 years showed a persistent and markedly abnormal sensitivity to a small dose of exogenous insulin with severe hypoglycaemia with convulsions, absence of clinical hyperadrenalism during hypoglycaemia, and a metabolic block in gluconeogenesis. The demonstration of a persistent biochemical abnormality of glucose metabolism at the age of 14 strongly suggests that ketotic hypoglycaemia of childhood is not another aspect of nutritional deprivation, as recently suggested (Buist, 1974), but the result of a defect in glucose homeostasis.

Introduction

Ketotic hypoglycaemia associated with convulsions was first described by Ross and Josephs in 1924. In their classical paper they described such a patient, established the relationship of ketotic hypoglycaemia to withdrawal of dietary carbohydrate and described the inability of adrenaline to raise the blood glucose during a hypoglycaemic episode. Over the ensuing years independent workers (mainly in the U.S.A.) confirmed the existence of this syndrome (Griffith, 1929; Rector and Jennings, 1937; Colle and Ulstrom, 1964; Habbick, McNeish and Stephenson, 1971; Chaussain, 1973), and the natural history has been accurately described.

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Following the description of the clinical syndrome and the realization that susceptible children were unable to maintain normal blood glucose levels under provocation with a ketogenic diet or with starvation, a defect in gluconeogenetic pathways or a deficit in the glucose precursor pool were suspected. Senior and Loridan (1969) found no abnormality in the pathways converting glycerol to glucose but Pagliara *et al.* (1972) demonstrated a block in the glucose-alanine cycle important in gluconeogenesis; low L-alanine levels were found in these patients and they fell even further after starvation or provocation with ketogenic diet. Intravenous L-alanine corrected both the hypoglycaemia and ketosis of an acute hypoglycaemic episode.

Recently there has been doubt whether this condition is a disease entity or one end of the normal spectrum (Buist, 1974). The patient described here demonstrates the persistence of a gluconeogenetic block from the age of 3½ to 14 years and lends support to the concept that ketotic hypoglycaemia of childhood may be an entity of its own.

Case history and results

A 15-year-old child was referred to the Medical Unit at the Royal Victoria Infirmary, Newcastle upon Tyne, for investigation of epilepsy and re-assessment of his endocrine status and carbohydrate metabolism in view of the prolonged and well documented attacks of hypoglycaemia in childhood. He was born in 1959 at 35 weeks' gestation with a birthweight of 5 lb. The mother had pre-eclampsia. All went well until the age of 3 years and 4 months when one morning at 06.45 hours the child was found convulsing. After an emergency hospital admission a lumbar puncture revealed a normal protein level and cell count. Unfortunately no glucose estimations were carried out. The child improved and the convulsion was attributed to a septic finger the child had for a week before admission. Four months later the child was admitted once more in status epilepticus having been found at

TABLE 1. Details of hospital admissions. Evidence for the syndrome of ketotic hypoglycaemia of childhood

Date	Age in years	Circumstances precipitating admission	Treatment before admission	On admission		Comments and investigations
				Urine acetone	Blood glucose	
24.6.62	3 ⁴ / ₁₂	6.45 a.m. found unconscious and convulsing. Two more fits in hospital the following morning	Immediate therapy—none	Not known	Not tested	—
18.10.62	3 ⁷ / ₁₂	9 a.m. convulsions following large vomit. Convulsions intermittently until 5 p.m.	Immediate therapy—none	Not known	4.30 p.m. 24 mg%	CSF glucose = 19 mg% GTT flat. No evidence of leucine sensitivity. Extreme sensitivity to insulin tolerance curve. Started on prednisone 5 mg daily
4.7.63	4 ⁴ / ₁₂	5 a.m. staring of the eyes with generalised convulsions. Repeated vomiting for 18 hr before admission	Immediate therapy—none	Not known	7.30 a.m. 28 mg%	i.v. glucose given in hospital with good effect. Discharged on prednisone 7.5 mg daily
28.8.63	4 ⁵ / ₁₂	Onset of drowsiness while playing. No convulsions	Glucose at home	Not known	100 mg	Prednisone increased to 5 mg b.d. 29.8.63 Fasting glucose 35 mg%
25.10.63	4 ⁷ / ₁₂	Onset of drowsiness and unresponsiveness	Glucose drink by mother. Sub-cutaneous adrenaline by G.P.	Not known	225 mg%	Prednisone increased to 5 mg t.d.s. Repeat GTT flat
17.12.63	4 ⁹ / ₁₂	Hypoglycaemic attack with drowsiness, slurred speech and convulsions 5 p.m.	Glucose drink at home	Not known	—	Fasting urine specimen 19.12.63 showed acetone+ Fasting blood glucose 18.12.63 58 mg%
1.1.64	4 ¹⁰ / ₁₂	5.45 p.m. unresponsiveness and twitching	Glucose drink. Glucagon intramuscularly by G.P.	Not known	9.10 p.m. 85 mg%	Acetonuria in fasting urine specimen over the next three days
12.2.64	4 ¹¹ / ₁₂	10 a.m. drowsiness with unresponsiveness	Intramuscular glucagon × 3 with no improvement	Not known	5.40 p.m. 40 mg%	Acetonuria the following day
27.6.64	5 ³ / ₁₂	Unconsciousness with unresponsiveness for 24 hr. Vomiting profusely for 12 hr before admission	Glucose drinks. Glucagon i.m. × 2. No effect	Acetone++	142 mg%	Plasma bicarbonate 15.9 mEq/l. Marked acetone in breath. 28.6.64 marked acetonuria
15.9.64	5 ⁶ / ₁₂	5.30 a.m. convulsions with drowsiness and vomiting	Oral glucose. i.v. dextrose by G.P.	Acetone+++	36 mg%	Fasting acetonuria over the following days. Treatment with prednisone 5 mg b.d. continued
27.10.64	5 ⁷ / ₁₂	Unresponsiveness with drowsiness following vomiting for 12 hr	i.v. dextrose	Acetone+++	Not tested	—
30.11.64	5 ⁸ / ₁₂	10 a.m. staring gaze with convulsions and ensuing drowsiness	Oral and i.v. glucose	No acetone present	165 mg%	Definite evidence of mental backwardness
1.1.65	5 ¹⁰ / ₁₂	Attack of measles	—	—	—	—
9.4.65	6 ¹ / ₁₂	Waiting list admission for repair of left inguinal hernia	—	—	—	Prolonged convulsions in hospital. Post op. (11.4.65) i.m. glucagon—No response. Marked acetonuria

Date	Age in years	Circumstances precipitating admission	Treatment before admission	On admission		Comments and investigations
				Urine acetone	Blood glucose	
11.8.65	6 ⁵ / ₁₂	6.30 a.m. convulsions	Glucose	Trace of acetone	109 mg%	—
9.11.65	6 ⁸ / ₁₂	7.30 a.m. convulsions with coma	Oral glucose	Acetone +++	30 mg%	—
13.10.66	7 ⁷ / ₁₂	7.45 a.m. convulsions with drowsiness	Oral glucose	Not known	199 mg%	—
28.11.66	7 ⁸ / ₁₂	6.45 a.m. convulsions	Oral glucose	Not known	—	—
8.9.67	8 ⁶ / ₁₂	6.45 a.m. convulsions with intermittent drowsiness	Oral glucose	Not known	9.30 a.m. 30 mg%	50 ml 50% i.v. dextrose. Confused for several hours. Completely well the following day. Treatment with prednisone 2.5 mg daily continued and stopped in April 1968. Started on phenobarbitone 30 mg b.d.
20.10.68	9 ⁷ / ₁₂	Rolling of eyes with drowsiness	Oral glucose	Not known	9.15 100 mg%	Phenobarbitone treatment stopped five days before admission. Attack most likely epileptic in nature

08.30 hours convulsing and vomiting. Blood glucose was 24 mg% and CSF glucose was 19 mg%. Intravenous glucose was given with effect. Over the next 6 years the child had a series of hospital admissions with episodes of hypoglycaemia (Table 1). During the first few admissions urine was not routinely tested, but later on acetonuria was found whenever the child was admitted hypoglycaemic. During these admissions, extensive endocrine investigations were carried out. The child was shown to be extremely sensitive to a small amount of exogenous insulin and during hypoglycaemia adrenaline was ineffective in raising blood glucose. By the age of 9 the hypoglycaemic attacks ceased, but attacks of minor epilepsy, characterized by rolling of the eyes, difficulty with focusing and transient loss of concentration, occurred at intervals. Less infrequently, he had grand mal attacks usually at night, with loss of consciousness and generalized convulsions. The child developed a behaviour disturbance with aggressive characteristics particularly evident at school.

On admission to the Medical Unit in September 1973 examination revealed a simple, retarded child. He had a mild stammer and the estimated developmental score was 6.5 years. His arm span was 158 cm, height 163 cm and pubis-to-ground length 80 cm. His secondary sex characteristics were well developed. Blood pressure was 115/75 mmHg, pulse 72 beats/

TABLE 2. Prolonged oral glucose tolerance test (50 g).

Time (hr)	0	$\frac{1}{2}$	1	1 $\frac{1}{2}$	2	2 $\frac{1}{2}$	3	4	5	6
Glucose (mg%)	84	86	94	82	80	78	74	70	70	68
Insulin (μ u/ml)	6	10	10	13	9	3	3	3	6	3

min and cardiovascular and respiratory systems were normal. Neurological examination revealed no abnormality. The haemoglobin was 13.7 g%, ESR 2 mm, serum iron 75 μ g%, iron binding capacity 315 μ g%, B_{12} level 380 pg/ml, folic acid 7.1 ng/ml, urea 28 mg%, serum creatinine 0.7 mg%, serum calcium 9.7 mg%, phosphate 4.7 mg%, alkaline phosphatase 230 u/l WR and VDRL negative. Chest skull X-rays were normal. Urinary amino-acid paper chromatography showed a mild, non-specific aminoaciduria. Two estimations of 24-hr urinary 17-hydroxy and oxosteroid excretion were normal (12.3, 10.8 mg, and 6.7, 5.4 mg respectively); 09.00 hours plasma cortisol 8.3 μ g%; 09.00 hours plasma ACTH 25 pg/ml; midnight plasma cortisol 3.3 μ g%; midnight plasma ACTH less than 15 pg/ml. Synacthen test was normal. Five day faecal fat was 4.5 g/day. A jejunal biopsy was normal. Electroencephalography showed an irregular and abnormal record compatible with diffuse cerebral damage, more marked on the right.

A prolonged oral glucose tolerance test (Table 2) showed a flat curve (in keeping with previous

TABLE 3. Intravenous glucose tolerance test (35 g).

Time (min)	0	10	20	30	40	50	60
Glucose (mg%)	68	158	114	90	80	78	74
Insulin (μ u/ml)	2	25	8	5	5	0	0

'k' value = 4.6%/min.

TABLE 4. Insulin sensitivity test (0.1 u/kg = 4 units), carried out at the age of 14 years.

Time (min)	0	30	45	60	90	120
Glucose (mg%)	84	< 20	< 20	< 20	< 20	< 20
Cortisol (μ g%)	8.9	10	16.2	18.2	19.8	2.30
A.C.T.H. (pg/ml)	66	65	130	110	105	178
Growth hormone (μ g/ml)	13	6.6	105	260	230	240

measurements). There was no reactive hypoglycaemia and only minimal secretion of insulin. Intravenous glucose tolerance test (Table 3) showed an early rise in glucose and insulin levels but they were at the lower limit of normal. The calculated 'k' value was 4.6%/min (Amatuzio, 1964). Normal range: 3.01-4.85%/min). An insulin tolerance test (Table 4) showed marked sensitivity to a small dose (0.1 u/kg) with prolonged hypoglycaemia. Clinically there was no evidence of hyperadrenalinism or hypoglycaemia until on completing the test the patient had a generalized convulsion quickly controlled with intravenous glucose and hydrocortisone. A glucagon test after a 12-hr fast did not produce any significant rise in glucose, or insulin release. A limited 26-hr provocation test with a ketogenic diet designed to provide 1200 cal/1.73 m² of body surface was carried out. There was no hypoglycaemia during the study but at 12 hr mild acetonuria appeared, increasing considerably at 24 hr. Intravenous L-alanine prepared, as described by Pagliara *et al.* (1972), was given over 15 min at 25.5 hr, and within 2 hr all acetonuria cleared.

Since the age of 9, no attack of hypoglycaemia has occurred and epilepsy is controlled with appropriate anticonvulsant therapy.

Discussion

The syndrome of ketotic hypoglycaemia appears to be the commonest cause of recurrent hypoglycaemic convulsions in children (Kogut, Blaskovics and Donnell, 1969; Chaussain, 1973; Christensen, 1974). The frequency of mental retardation, epilepsy, and brain damage with all the physical and social sequelae has been reported as over 30% (Kogut *et al.*, 1969). This emphasizes the importance of early diagnosis and management for it seems that this is a treatable condition. Low birthweight children are preferentially affected, onset is usually between the ages of 2 and 5 years and spontaneous improvement occurs by the age of 8-9 years (Habibick *et al.*, 1971; Pagliara *et al.*, 1973). The reason

why the syndrome becomes clinically evident between the ages of 2 and 5 and gradually settles by the age of 9 is still not well understood. Senior and Loridan (1969) thought that the amelioration with growth could reflect an increase in size of the pool of glucose precursors and noted that a similar amelioration with age occurs in type III glycogenosis despite the persistence of the enzymatic disorder.

The glucose-alanine cycle is an important mechanism for gluconeogenesis and may act as an end-pathway through which many other factors operate to contribute to gluconeogenesis (Felig, 1973). The demonstration of an abnormality in the glucose-alanine cycle with low, depleted, basal L-alanine levels and rapid reduction during provocation with a ketogenic diet and insulin is important in explaining the undue sensitivity exhibited by such patients to small doses of exogenous insulin. As early as 1937, Hartmann, Jaudon and Morton commented on the striking intolerance to insulin of this group of patients and reported that in two of their patients hypersensitivity to insulin persisted for 3 years after the first examination. In our patient this abnormality persisted to the age of 14 and injection of a small dose of insulin (0.1 u/kg) resulted in a convulsion. Similar findings, also with generalized convulsions, were found by Broberger, Jungmer and Zetterstrom (1959) in three children. In our patient, all other hormonal reactions, including ACTH release, cortisol and growth hormone responses, appeared normal (Table 4). Broberger *et al.* (1959), Köffler, Schubert and Hug (1971) and Christensen (1974) also demonstrated failure of adrenaline secretion during an insulin provocation test, and this observation could explain the clinical observation of lack of any clinical signs before the onset of convulsions during such a test, in the presence of severe hypoglycaemia. This observation is of great importance, for knowledge of this discrepancy between the presence of hypoglycaemia and the absence of clinical symptoms should ensure that such children are not left in prolonged hypoglycaemia often with detrimental results. If ketotic hypoglycaemia is suspected and an insulin sensitivity test is thought to be necessary, a smaller dose of insulin—such as 0.05 u/kg—should be used to minimize the dangers of excessive hypoglycaemia. The explanation of the failure of adrenaline response has until recently remained a puzzle. Goodall, Cragan and Sidbury (1972) thought that delayed maturation of the adrenal medulla was a likely explanation but clearly this is now unacceptable since the abnormality persists until after puberty. Tietze *et al.* (1972) favoured a central neurological hypothalamic explanation but again no convincing evidence of such an abnormality is available. Flatbush *et al.* (1974) have recently shown that in the presence of ketosis adrenaline secretion is impaired. These

workers were able to show that in anaesthetized dogs adrenaline secretion after insulin stimulation could be prevented by infusion of ketone bodies to sustain a blood ketone concentration of 1–2 mmol/l. Earlier Drennick, Alvarez and Tamasi (1972) in a study involving insulin sensitivity tests in obese patients before and after starvation noted a marked failure of adrenaline secretion during the repeat insulin sensitivity test. The mean β -OH butyrate plasma concentration was 8.02 mmol/l. During the second insulin sensitivity test, hypoglycaemia was more severe but clinically silent. These experimental findings reproduce some of the findings in patients with ketotic hypoglycaemia of childhood and add weight to the possibility that the presence of ketosis may be responsible for the failure of adrenaline secretion and clinically silent hypoglycaemia. There is, therefore, evidence that ketotic hypoglycaemia of childhood is the result of an abnormality of glucose homeostasis, mainly involving the rate of production of L-alanine in the peripheral muscle and thus interfering with gluconeogenesis and the ability to maintain adequate blood glucose levels.

Reports during the last 50 years, mainly restricted to the U.S.A. and Europe, of children from different family backgrounds and nutritional status, make it unlikely that this syndrome is the result of nutritional deprivation. The episodes of hypoglycaemia appear to be the result of a basic defect in gluconeogenesis in the presence of an otherwise normal endocrine system and the associated ketosis, a useful clinical marker, may be responsible for the failure of adrenaline secretion and clinically silent hypoglycaemia.

Conclusion

A patient with ketotic hypoglycaemia of childhood and mental retardation due to uncontrollable episodes of hypoglycaemia is described. For the first time, a basic abnormality of glucose homeostasis has been demonstrated persisting from the age of 3 years and 7 months to the age of 14, 5 years after spontaneous episodes of hypoglycaemia ceased. This finding suggests that nutritional deprivation is a very unlikely cause of this syndrome, although it could on occasions be responsible for aggravating the tendency to hypoglycaemia and thus precipitate attacks of hypoglycaemia.

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