A case of leucine-induced hypoglycaemia

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It was first reported in 1956 (Cochrane, Payne, Simpkiss, and Woolf) that the essential amino acid leucine was the cause of a fall in blood sugar in some hypoglycaemic infants whose convulsions were exacerbated by a high protein/low carbohydrate diet. Subsequently it has been found that many infants with idiopathic hypoglycaemia are sensitive to leucine (Mabry, DiGeorge, and Auerbach, 1960; Cochrane, 1960; Fajans, 1965). Good reviews of this subject have been written by Cornblath and Schwartz (1966) and by Cornblath (1968). The incidence of mental retardation and neurological sequelae in such cases of leucine-induced hypoglycaemia is high. Early diagnosis and adequate treatment are therefore imperative, particularly since diazoxide, a benzothiadiazine non-diuretic antihypertensive drug, is found to be partially or completely effective in maintaining the blood sugar within the normal range (Drash and Wolff, 1964; Samols and Marks, 1966).

Clinical manifestations occur usually before the age of 8 months, presenting often with postprandial convulsions. Mental retardation becomes progressively more obvious as the child grows older.

We present below another case of leucine-induced hypoglycaemia studied both clinically and, after death, pathologically. Pathological observations in similar cases have not hitherto been published.

CASE HISTORY

The patient, K.C., was illegitimate, born to a healthy girl of 16 years. There are no known siblings and nothing is known about the father. The pregnancy was normal and supervised; spontaneous normal delivery after episiotomy occurred at full term, when there was a slight rise in blood pressure to 140/95 mm Hg. The infant was healthy with a birth weight of 2-75 kg. The blood group of the mother was O Rhesus negative and no antibodies were present. There were no neonatal complications and mother and baby were discharged on the tenth day. Feeds were taken well and the baby was transferred from breast to bottle feeding with dried cows' milk on the third day. He was then given Ostrermilk, and cereals were started at 6 weeks of age. He fed and slept well and weight gain was satisfactory.

He was examined and passed as suitable for adoption and placed with prospective adoptive parents at 3 months old, where he continued to develop normally until the age of 4 months. He then began to have abortive grand mal attacks several times a day, usually before or after a meal. At that time he weighed 6-30 kg and the head circumference was 40-6 cm, both figures being within normal limits.

Initial full investigation of this child at 5 months of age revealed an apparently normal, fit-looking baby, whose EEG showed no abnormality. Low blood sugars of 24 mg/100 ml. and 35 mg/100 ml. were obtained during convulsions. Fasting blood sugars were also consistently low. A glucose tolerance test showed a large increase from a low fasting level, and tests for L-leucine sensitivity demonstrated an exacerbation of the hypoglycaemia with a normal response to glucagon. An oral leucine load, given after the fasting blood sugar level had been increased by glucose, was followed by a greater than 50% reduction in blood sugar one hour later (see appendix for results). He was transferred to another hospital where further tests confirmed the tendency to hypoglycaemia on fasting, exacerbated by L-leucine and rectifiable by glucagon.

Investigations yielding normal results included a radiograph of the skull and chest, examination of amino acids in the urine, toxoplasma dye test (negative at 1 in 4), full blood count, blood urea and electrolytes, blood calcium, phosphates and alkaline phosphatase, WR and Kahn, and cerebrospinal fluid. Excretion of urinary phosphate and calcium was normal. Tryptic activity was present in stools in a 1 in 800 dilution.

A diagnosis of leucine-induced hypoglycaemia was made and the patient was treated with methyl prednisolone and extra glucose two hours before and after normal feeds. He appeared well controlled on this regime and remained initially free from convulsions, but had several fits with a fever at 8 months. At 9 months an EEG was again normal.1. Random blood sugar estimations during the rest of his life were in the low normal range and he remained somewhat sensitive to leucine despite steroids.

Numerous readmissions to hospital followed for intercurrent infections, including dysentery and chicken pox. During the latter illness the prednisolone was reduced and despite this he was free from convulsions. At the age of 1 year his weight was 9-07 kg, between the 10th and 25th percentile.

Physical and mental progress was slow and he remained in a nursery as he was not considered suitable for adoption. At the age of 19 months psychological assessment placed his sensorimotor abilities on the Piaget scale of development at the 3 to 9 months old level, although his locomotor and dressing attainments were normal and
feeding attainments only slightly retarded, he was clearly retarded in sensorimotor development, oculomotor co-ordination, and speech.

At 24 months he was re-admitted to hospital and again at 28 months, after fits. His weight was then 9.20 kg, below the 3rd percentile, and his height 79.7 cm, also below the 3rd percentile. He had gross cushingoid features, was hirsute, euphoric, and had striae on the abdomen (Fig. 1). He remained on corticosteroids (methyl prednisolone 2 mg twice daily).

When examined at 52 months he weighed 10.65 kg; his height was 84 cm. His blood pressure was 125/80 mm Hg, his teeth were malpositioned, and neurological examination revealed no abnormality. Psychological assessment of his functional attainments placed him well within the severely subnormal range. He had no speech, was not toilet-trained, could not finger feed or use a spoon, could sit, stand, and run, and occasionally responded to his name. There was no evidence of regression of abilities at any time, development having been very slow from the first year of life. EEGs while awake and asleep were again within normal limits. Radiograph of the spine showed flattening of the vertebrae and the bone age was 18 months.

His blood sugar levels remained fairly well controlled with corticosteroids and additional glucose. Nevertheless, it was decided to withdraw steroids under ACTH cover because of the unacceptable side effects and to replace them with diazoxide, 50 mg twice daily. Initially, the child appeared to be clinically improved. The urine remained free from sugar and ketosis did not occur. However, four weeks after the diazoxide was started he developed sticky eyes and otitis media followed by measles three weeks later. Despite antibiotics, an increase in the dose of diazoxide, and reintroduction of steroids, he developed a fulminating illness and died with pneumonia and sudden cardiac arrest seven days after the rash appeared.

Necropsy

Necropsy was performed 45 hours after death. The child was rather fat and small for age (height 86 cm, weight 12.68 kg). He was moon-faced and showed generalized hirsutism. A fading morbilliform rash and fine scaling were present over the face, forearms, and hands. Both lungs showed generalized bronchopneumonia. The cut surface of the liver (522 g) was pale yellow in colour. The pituitary weighed 0.27 g. The adrenals were small, weighing 1.8 g and 2.0 g. The spleen weighed 46 g. The brain weighed 1.130 g and presented no macroscopic abnormality other than flattening of the convolutions and uncinate grooving. The cerebellum and the brain-stem were also normal in size, weighing together 154 g.

Histological Findings

Blocks of the testes, thymus, pituitary, pancreas, adrenals, lungs, heart, thyroid, liver, kidney, sciatic nerve, spleen, bone marrow, colon, ileum, muscle, parotid, bladder, and skin were embedded in paraffin and sections examined after staining with haematoxylin and eosin and HVG.

![Fig. 1. Front and back of patient, aged 28 months.](http://jnnp.bmj.com/)

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Frozen sections of the liver were stained for fat and with PAS before and after treatment with diastase. Other frozen sections of the liver were stained with Sudan III before and after treatment with fat solvents—that is, absolute alcohol and chloroform. Blocks from all representative levels of the central nervous system were embedded in celloidin and sections stained with cresyl violet, HVG, by the Heidenhain method for myelin and the Holzer method for fibrous glia. Frozen sections of the cerebral cortex and white matter were stained by the Holzer method for fibrous glia, the Gros-Bielschowsky method for myelin, and by the Hortega and Cajal methods for astrocytes.

The most conspicuous and unequivocal neuropathological change was fibrous gliosis of the white matter of the cerebral hemispheres, cerebellum, and brain-stem, seen best in sections stained by the Holzer method (Figs. 2 and 3). Cellular stains showed astrocytic overgrowth and hyperplasia in the gliotic areas but there was no visible diminution or staining anomaly of myelin; nor was there any significant increase in the amount of sudanophil material.

In comparison with the above anomaly, all others seemed to be terminal, questionable, or marginal. The number of glial cells in the subpial layer of the cerebral cortex was possibly increased. Some neurones in the cerebral cortex showed pallor of staining and others had almost completely faded. A relatively acellular zone was present around some blood vessels. Some naked hypertrophied astrocytic nuclei of Alzheimer type II were seen in the cerebral cortex.

The cerebellum showed a slight astrocytic overgrowth in the molecular layer and a minimal focal loss of Purkinje cells with proliferation of the Bergmann glia. The spinal cord presented no abnormality.

The lungs showed confluent massive bronchopneumonia. The cortex of the thymus was largely depleted of lymphocytes and the development of Hassal's corpuscles was slight. The liver showed marked fatty change. Most of the Kupffer cells were enlarged and contained PAS positive material. This material was sudanophil and completely soluble on treatment with fat solvents. Some histiocytes in the spleen and bone-marrow contained similar material. The skin showed parakeratosis. Collections of histiocytes, lymphocytes, and a few...
polymorphs were present in the papillary layer and around some blood vessels in the dermis. In spite of their low weight the adrenals were histologically normal. The pancreas was normal in size (21 g) and showed no histological abnormality.

**DISCUSSION**

A good deal has been written about the neuropathological changes associated with hypoglycaemia in adults (Meyer, 1963) but very little is known about the pathology of hypoglycaemia in infants and children. Neuropathological findings in a group of hypoglycaemic infants have been described by Anderson, Milner, and Strich (1966). The untreated cases of their series showed marked degenerative changes in nerve cells throughout the central nervous system. In small nerve cells the nuclear membrane was indistinct or absent and there was clumping or breaking up of the nuclear chromatin. Many large neurones showed chromatolysis and their nuclei were shrunken, opaque, and finely stippled. Some motor neurones in the brain-stem and spinal cord were vacuolated. These cases had run, unlike the present one, a rather acute course, the oldest being 6 months old at the time of death, and the findings may not be like those in chronic cases. Leucine sensitivity was not established in any of their cases.

Although the prognosis is known to be unfavourable in cases of infantile hypoglycaemia, it is not yet certain whether the associated encephalopathy is a complication of hypoglycaemia, its cause, or a manifestation of still another factor responsible for both encephalopathy and hypoglycaemia. That the nervous system is in some cases deranged before the onset of hypoglycaemia has been suggested by Knobloch, Sotos, Sherard, Hodson, and Wehe (1967) and Ingram, Stark, and Blackburn (1967). There is no evidence from the history available that the present case suffered significant perinatal injury or jaundice, and subsequent investigations suggested a causal role for leucine-induced hypoglycaemia in the development of his severe mental handicap. The convulsions were fairly well controlled by corticosteroids and supplementary glucose—at the expense, however, of the onset of cushingoid signs and failure of physical growth.

The main neuropathological abnormality in the present case—namely, fibrous gliosis of the white matter without associated loss of myelin—is an entirely non-specific change found often in cases of severe subnormality with and without associated metabolic disorder (Crome and Stern, 1967). It may be present already at birth or appear in the course of infancy. It is impossible, therefore, to decide whether it is the consequence or the cause of hypoglycaemia. Neither do our data establish whether the brains of leucine-sensitive hypoglycaemic infants are still normal at birth. It may be significant, however, that lesions usually attributed to post-natal hypoglycaemia, or epilepsy, such as selective degeneration of the grey matter and sclerosis of the hippocampus and cerebellum, were absent in the present case.

We are unable to explain fully the accumulation of adventitious material in some cells of the reticuloendothelial system. By its staining properties the material was a glycolipid. Since neither the liver nor the spleen was enlarged and no lipid storage was present in the nervous system it is unlikely that the storage was long-standing feature of the condition. It is perhaps best explained as a reaction to the terminal infection to which the patient succumbed.

**SUMMARY**

A seemingly healthy boy developed convulsions at 4 months and was found to have a chronic hypoglycaemia exacerbated by fasting and L-leucine. He made a partial biochemical response to corticosteroids, his fits were partially controlled, but he developed cushingoid features and was severely retarded physically and mentally. At the age of 54 months an attempt was made to substitute diazoxide for the corticosteroids but the patient died from intercurrent measles and pneumonia. The main neuropathological change was fibrous gliosis of the white matter without demyelination.

The patient was treated and studied in life by many physicians and pathologists, to all of whom we are grateful for access to records. We are indebted particularly to Dr. Jan Stern and Dr. Vincent Marks for their help in the treatment of the case, and to Dr. H. M. T. Coles, under whose care the patient was at this and another hospital, for permission to publish.

**APPENDIX**

The results of tests carried out at 5 months of age before treatment with corticosteroids began were as follows.

1. **GLUCOSE TOLERANCE TEST**
   - Fasting blood sugar: 19 mg/100 ml.
   - Ingestion of 10 g glucose
     - 30 min later blood sugar 112 mg/100 ml.
     - 60 " " 112 "
     - 90 " " 78 "
     - 120 " " 67 "
     - 170 " " 22 "

2. **ORAL L-LEUCINE SENSITIVITY TEST**
   - Loading dose 150 mg L-leucine/kg body weight
   - Fasting blood sugar 22 mg/100 ml.
   - 55 min later 15·5 mg/100 ml.
   - 90 " < 5 "
Intramuscular glucagon then raised blood sugar to 94 mg/100 ml after 11 min.

3. ORAL L-LEUCINE SENSITIVITY TEST WITH GLUCOSE

Fasting blood sugar 38 mg/100 ml.
10 g glucose given
40 min later blood sugar 92 mg/100 ml.
150 mg L-leucine/kg body weight given orally in milk
60 min later blood sugar 41 mg/100 ml.

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