Leigh’s Encephalomyelopathy: an Inborn Error of Gluconeogenesis

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In 1951 Leigh described a condition which is now known as subacute necrotizing encephalomyelopathy. Ebels, Blokzijl, and Troelstra (1965) have summarized findings in 28 of these patients, all of whom died. Since then 6 further cases have been described by Worsley et al. (1965), Namiki (1965), Lakke, Ebels, and ten Thye (1967), and Clayton, Dobbs, and Patrick (1967).

The metabolic background of this syndrome is not yet established. The biochemical abnormalities recorded have been (1) a persistently low plasma bicarbonate level, noted by Feigin and Wolf (1954) and confirmed in the 2 cases of Worsley et al. (1965), and (2) high blood pyruvate and lactate levels observed in the 2 cases of Worsley et al. (1965) and in the cases described by Clayton et al. (1967). Recently, Clayton et al. (1967) (see also Crome and Stern, 1967) have reported treatment of this condition with lipoic acid, with some clinical benefit, as was also seen in the present case.

This paper describes a deficiency of the enzyme pyruvate carboxylase in the liver of a patient with this condition.

Methods

Glucose was determined by the method of Hagedorn-Jensen as used in the Technicon Autoanalyzer. Lactate and pyruvate were determined enzymatically according to Bergmeyer (1963). Semiquantitative screening for aminoaciduria was conducted by high voltage electrophoresis on paper (Clotten and Clotten, 1962). The liver biopsy, which was obtained with a Menghini needle, was homogenized in a Potter-Elvejhem homogenizer, with 10 mM tris hydroxyethylaminomethane buffer, pH 7·5, containing 2 mM EDTA.

The homogenate was used for the determination of phosphoenolpyruvate carboxykinase activity which was assayed as described by Nordlie and Lardy (1963), and pyruvate carboxylase activity which was determined according to Utter and Keech (1963).

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Case Report

The patient is a brother of Case 3 described by Ebels et al. (1965). He is the youngest of 7 children, 3 of whom died with the picture of progressive mental retardation, starting at an age varying from 3 to 6 months. He was born in June 1966, of healthy unrelated parents. At an uncomplicated pregnancy and delivery, birth-weight 2·62 kg., length 53 cm. Progress was uneventful until at the age of 4 months he developed vomiting and diarrhoea, which led to hospital admission. Routine blood chemistry and urine analysis revealed no abnormalities. At 6 months, a slight, general, aminoaciduria was found (282 μmoles amino acids excreted/kg. per 24 hr.), as had also been noted in an elder brother who had died. At this stage there was still no abnormality in the physical and mental development, and all symptoms disappeared after simple dietary treatment for the diarrhoea.

He was admitted to hospital again at the age of 11 months because of failure to thrive. He had been vomiting for a few weeks, with episodes of anorexia, irritability, and lethargy, and now seemed to be mentally retarded.

His weight was 5·86 kg., length 71 cm., skull circumference 43 cm. He was slightly dehydrated; there was rolling of the eyes, as illustrated in the paper by Clayton et al. (1967); and he was unable to sit. The muscles were hypotonic, and tendon reflexes were depressed. EEG showed epileptic activity on the right temporal site. Echo encephalogram: mid structure displaced 3 mm. to the left. Plasma: bicarbonate 21 mEq/l.; sodium, chloride, potassium, urea, alkaline phosphatase, acid phosphatase, phosphate, calcium, and magnesium, normal. Blood: pH 7·54, glucose 46 mg./100 ml. Electrophoresis of serum proteins normal. Urine: a slight general aminoaciduria was again found (240 μmoles of amino acids excreted/kg. per 24 hr.). CSF glucose was low (37 mg./100 ml., normal 50–70 mg./100 ml.), and protein raised (95 mg./100 ml.).

Glucose tolerance test was normal, except for a somewhat low fasting value (64 mg./100 ml.) (Fig. 1). The response to intramuscular injection of glucagon and epinephrine was normal (Fig. 2). Blood lactate and pyruvate levels were 30 ·4 mg. and 4 ·4 mg./100 ml.,
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respectively, and these did not change during the glucose tolerance test (Fig. 1) (normal values 15 mg. and 0·5 mg./100 ml., respectively). These high values of blood lactate and pyruvate, combined with the low fasting blood glucose levels, suggested an impaired rate of gluconeogenesis, and it was decided to assay the liver enzymes responsible for the entrance of pyruvate into the gluconeogenetic pathway, pyruvate carboxylase, and phosphoenolpyruvate carboxykinase.

The activity of phosphoenolpyruvate carboxykinase was 3·4 µmoles of oxaloacetate converted to phosphoenolpyruvate per minute per g. wet weight (Table), which is well within the range of enzyme activities of gluconeogenesis as given by Krebs (1963).

The specific activity of pyruvate carboxylase was 3 × 10^{-3} µmoles per minute per gram wet weight (Table). This value is only 1/1000th of the value found in adult rat liver or in liver from human controls of the same age-group. (Specimens of human liver were obtained by open surgery from 2 patients with congenital anatomical disorders with hepatomegaly.) The normal value for phosphoenolpyruvate carboxykinase in the liver biopsy of our patient as compared with the controls (Table) makes it likely that a representative sample of liver has been biopsied.

**Treatment.** Lipoic acid was used, as suggested by Clayton *et al.* (1967), at a dose rate of 0·7 mg./kg., intramuscularly 3 times a week. The effect of treatment on blood lactate and pyruvate levels is shown in Fig. 3. Two weeks after the start of treatment, the child's general condition was considerably improved. During the 5 weeks of treatment his weight increased from 5·9 to 7·1 kg., his length from 72 to 76 cm., and his head circumference from 43 to 44·2 cm. Signs of dehydration disappeared, as did the vomiting. He became less drowsy and more interested in his surroundings. Motor development, however, remained retarded, and he was unable to sit alone. The abnormal eye movements persisted. He learnt to speak a few words and it seemed that intellectual development was less retarded than motor development.

Two weeks after starting lipoic acid treatment, blood lactate had fallen to the upper limit of normal. In the course of the following four weeks, lactate rose again to pathological values (Fig. 3). However, omission of lipoic acid resulted in a further sharp increase, with a decrease again when lipoic acid was restarted. Increased physical exercise, with its resulting peripheral lactate production, was now suspected of contributing largely to the high blood lactate level, and exercise was therefore curtailed. In the following 2 weeks blood lactate fell again to the upper limit of normal. When physical exercise was reinstituted the blood lactate rose once more, decreasing again to its previous value when it was curtailed (Fig. 3).

**TABLE**

Activities of Phosphoenolpyruvate Carboxykinase (PEP-C) and Pyruvate Carboxylase (Pyr-C) in Liver of Rat, Normal Controls, and Patient

<table>
<thead>
<tr>
<th>Activities (µmole/min. per g. wet weight)</th>
<th>PEP-C</th>
<th>Pyr-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult rat liver</td>
<td>1·9</td>
<td>3·0</td>
</tr>
<tr>
<td>Control I, aged 14 days</td>
<td>3·7</td>
<td>2·1</td>
</tr>
<tr>
<td>Control II, aged 1 year</td>
<td>4·8</td>
<td>6·2</td>
</tr>
<tr>
<td>Patient</td>
<td>3·4</td>
<td>3 × 10^{-3}</td>
</tr>
</tbody>
</table>

**Fig. 1.**—Glucose tolerance curve of patient after oral administration of glucose 2 g./kg. as a 10% solution. The blood lactate and pyruvate levels are also shown.

**Fig. 2.**—Blood glucose levels after intramuscular injection of glucagon 0·03 mg./kg. (-- -- --) and after intramuscular injection of 1 mg. epinephrine (--- --- --).
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Discussion

Three other children in this family died with the same symptoms. In one a diagnosis of Leigh's encephalomyelopathy had been made (Ebels et al., 1965), and the child described here must be assumed to be suffering from the same disorder. The finding of an almost total lack of pyruvate carboxylase activity in the liver makes it likely that this inborn error of metabolism is due to a lack of this enzyme. The fact that the activity of the enzyme phosphoenolpyruvate carboxykinase in liver was normal, confirmed that a representative sample of liver was obtained for enzyme assay. It also shows that the absence of pyruvate carboxylase activity was not accompanied by any general fall in activity of enzymes of gluconeogenesis.

Lactate, produced in peripheral tissue by glycolysis, is partly reconverted to glucose in the liver, and to a minor extent in some other tissues, such as kidney cortex. This process, known as gluconeogenesis, involves initially the chain of reactions shown in Fig. 4. The absence of pyruvate carboxylase, as observed in this patient, could account for the persisting high pyruvate and lactate levels from blockage at the step where oxaloacetate is formed from pyruvate. It could also account for the low blood glucose level, because gluconeogenesis is greatly impaired, though, owing to the existence of alternative pathways (e.g. involving malate) for the production of oxaloacetate, it is not abolished.

Worsley et al. (1965) have attributed the high values of blood lactate and pyruvate in this condition to a higher rate of glycolysis, rather than to an impaired rate of gluconeogenesis. A normal rate of glycolysis is evident from the normal glucose tolerance curve in both ours and Worsley's patients, and from the normal response to glucagon and epinephrine.

The beneficial effects of lipoic acid, as reported by Clayton et al. (1967) and Crome and Stern (1967), were confirmed in our case. The effects of physical exercise demonstrated, however, that lipoic acid failed to correct completely the depressed rate of lactate utilization, for blood lactate then rose to pathological levels despite lipoic acid therapy. Lipoic acid would not be expected to correct the disturbed lactate utilization completely, because it is not involved in the pyruvate carboxylase reaction. Its mode of action must therefore be sought in some other metabolic route.

It is not clear how this enzyme defect causes severe degeneration of brain tissue during the first year of life (Leigh, 1951; Ebels et al., 1965). A high pyruvate level might interfere with the metabolism of glutamic acid, notably transaminase reactions. Rolleston and Newsholme (1967) have recently demonstrated that lactate at a concentration of 5 mM (43 mg./100 ml.) inhibits glycolysis of brain cortex. Further experiments are needed to determine whether this can give rise to the extensive brain damage seen in this condition.

Summary

A 1-year-old boy is described, with a clinical picture suggestive of Leigh's encephalomyelopathy.

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**Fig. 3.**—Effect of intramuscular lipoic acid treatment (0.7 mg./kg., 3 times a week), on blood lactate and pyruvate concentration.

**Fig. 4.**—Initial steps of gluconeogenesis. Pyruvate is converted, by the enzyme pyruvate carboxylase, to oxaloacetate, which is subsequently converted to phosphoenolpyruvate by the enzyme phosphoenolpyruvate carboxykinase.
3 sibs had previously died with a similar clinical picture, and in one of these necropsy confirmed the presence of brain lesions characteristic of Leigh's syndrome.

The main biochemical finding was a high level of pyruvate and lactate in the blood. Glucose levels in blood and CSF were slightly low. A normal rate of glucose utilization was inferred from the normal glucose tolerance test, and from the normal rise in blood glucose after injecting glucagon or epinephrine. It was concluded that there was an impaired rate of gluconeogenesis.

In liver tissue obtained by biopsy there was almost complete absence of the enzyme pyruvate carboxylase which is responsible for the conversion of pyruvic acid to oxaloacetic acid in the process of gluconeogenesis. It is suggested that Leigh's syndrome may be the result of a lack of pyruvate carboxylase.

Treatment with lipoic acid resulted in some clinical improvement, and in some reduction in the abnormal lactate blood levels.

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