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Congenital lacticacidemia caused by lipoamide dehydrogenase deficiency with favorable outcome

O. N. Elpeleg, MD, W. Ruitenbeek, PhD, C. Jakobs, PhD, V. Barash, PhD,
D. C. De Vivo, MD, and N. Amir, MD

From the Metabolic and Neuropediatric Units, Shaare-Zedek Medical Center, Jerusalem, Israel, the Department of Pediatrics, University Hospital, Nijmegen, The Netherlands, the Department of Pediatrics, Free University Hospital, Amsterdam, The Netherlands, the Department of Clinical Biochemistry, Hadassah Medical Center, Jerusalem, Israel, and the Department of Neurology, Columbia Presbyterian Medical Center, New York, New York

A 5-year-old boy had recurrent vomiting and lethargy with lacticacidemia and ketoacidemia since birth. Lipoamide dehydrogenase deficiency was found in muscle and fibroblasts. Therapy with sodium dichloroacetate, thiamine, and carnitine was associated with reduction of the severity and frequency of the decompensation episodes and near normal plasma lactate levels. At 5 years of age, the patient has normal cognitive function and moderate motor impairment. (J PEDIATR 1995;126:72-4)

Inborn errors of metabolism associated with combined lacticacidemia and ketoacidemia usually cause life-threatening metabolic decompensation in infancy. In many cases the primary enzymatic defect can be localized to the pyruvate dehydrogenase complex or to the mitochondrial respiratory chain. The most common defect in the PDHC resides in its E1 subunit; deficiency of the E3 subunit (lipoamide dehydrogenase) has been reported in only a few patients,¹⁻⁵ whose clinical course was characterized by progressive neurologic deterioration; most died during early childhood.

We describe a 5-year-old boy with LAD deficiency who has been treated for the past 3 years with sodium dichloroacetate, thiamine, and carnitine. His cognitive functions were age appropriate, but his motor development was moderately impaired.

CASE REPORT

A 7-month-old boy was admitted because of refusal to eat and recurrent vomiting for 24 hours. He was the third child of nonconsanguineous Ashkenazi-Jewish parents. Two older sisters were healthy. He was born in another hospital after an uneventful pregnancy and delivery; birth weight was 4000 gm. He had an episode of tachypnea and vomiting 12 hours after birth, with a plasma lactate concentration of 7.0 mmol/L (normal, <2.4 mmol/L) and total ketone bodies of 1.27 mmol/L (normal, <0.24 mmol/L).

Submitted for publication March 17, 1994; accepted Aug. 24, 1994.

Reprint requests: Orly N. Elpeleg, MD, Metabolic Unit, Shaare-Zedek Medical Center, Jerusalem 91031, Israel.

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0022-3476/95/\$3.00 + 0 9/22/60180

Thereafter he was hospitalized every 6 to 8 weeks for loss of appetite, recurrent vomiting, and hyperlactatemia (Figure). Thiamine, riboflavin, coenzyme Q, and biotin were given for a suspected mitochondrial disorder. None of these agents had reduced the frequency of the attacks.

Physical examination revealed tachycardia, tachypnea, pallor, hepatomegaly, and muscle hypotonia. Blood pH was 7.15, partial pressure of carbon dioxide 19 mm Hg, plasma lactate concentration 9.8 mmol/L, and total ketone bodies 6.61 mmol/L. Plasma carnitine concentration was 21.8 μ mol/L (normal, \geq 30 μ mol/L).

DCA	Sodium dichloroacetate
LAD	Lipoamide dehydrogenase
NADH	Nicotinamide adenine dinucleotide (reduced form)
PDHC	Pyruvate dehydrogenase complex

Serum aspartate aminotransferase activity was 10,000 IU/L (normal, < 50 IU/L), alanine aminotransferase 12,000 IU/L (normal, < 56 IU/L), and prothrombin time 40% of the control value. Creatine kinase activity was normal. Plasma amino acid values were normal except for an increased alanine concentration. Cerebrospinal fluid lactate concentration was 1.4 mmol/L. Abdominal ultrasonography revealed liver and kidneys of normal size. Findings of echocardiography and cranial computed tomography were normal. The patient gradually improved after intravenous administration of glucose and Na bicarbonate solution. However, when he was clinically well, plasma lactate concentration and ketone bodies remained elevated. Open muscle biopsy was performed with the patient under general anesthesia, and muscle tissue was obtained from the right quadriceps. Electron microscopic findings, including mitochondrial size and shape, were normal. The main portion was immediately frozen at -70° C for enzymatic analysis.

Similar episodes during the following 2 months were accompa-

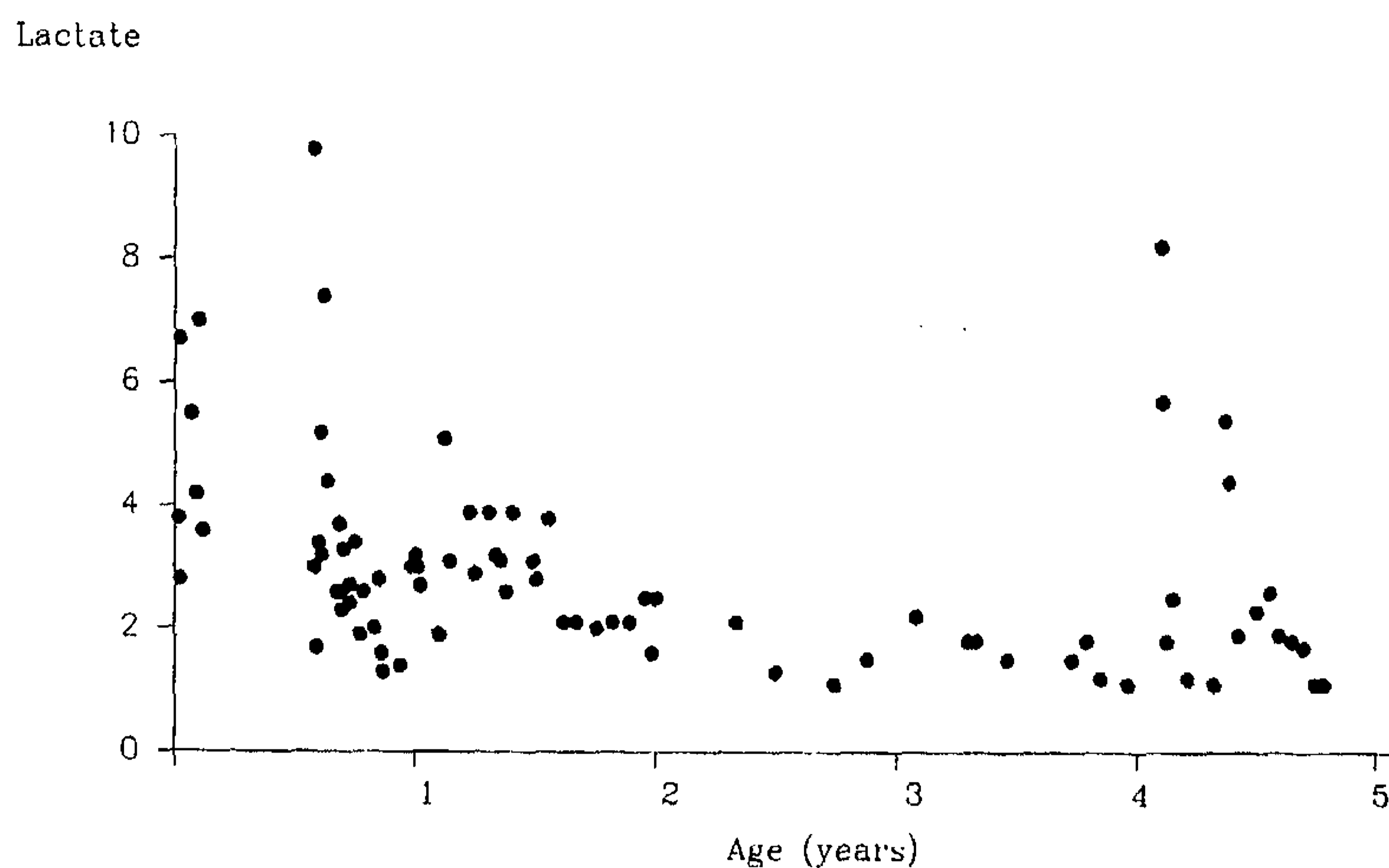


Figure. Lactate concentration (in millimoles per liter) as a function of year of life. Therapy was started at 9 months of age. The increased lactate concentrations after 4 years of age were associated with the discontinuation of DCA administration.

nied by moderate neurologic deterioration with severe generalized hypotonia and inability to sit unsupported. A therapeutic trial with DCA, carnitine, thiamine, lipoic acid, Na succinate, and restriction of branched-chain amino acids was initiated. This regimen was associated with normalization of plasma lactate values, but plasma ketones remained elevated.

Since 2 years of age the patient had been treated with DCA, thiamine, and carnitine. In addition to his regular oral intake, supplementary nasogastric feeding was maintained because of periods of anorexia. During the second year he had only four episodes of recurrent vomiting in association with elevated liver transaminase values, moderate hyperketonemia, and nearly normal plasma lactate levels. No such episodes were noted thereafter. Repeated attempts since 4 years of age to reduce DCA dosage to less than 25 to 30 mg/kg every 12 hours resulted in hyperlactatemia (Figure). At 5 years, the patient's weight was at the 50th percentile, length at the 75th percentile, and head circumference at the 50th percentile. The patient had hepatomegaly and general muscular hypotonia. He walked freely on a broad base, comprehension was age appropriate, and he spoke fluently. Cranial computed tomography, electroencephalography, electromyography, nerve conduction velocity, visual evoked potentials, electroretinography, electrocardiography, echocardiography, and abdominal ultrasonography, performed every year, showed results within the normal range.

METHODS

Plasma lactate levels were determined in 15 samples before therapy was started and in 66 samples during therapy. Urinary organic acids were identified with a Hewlett-Packard 5970 mass selective detector as previously described.⁶

In muscle homogenate, the activities of rotenone-sensitive NADH:ubiquinone oxidoreductase, antimycin-sensitive succinate:cytochrome *c* oxidoreductase, cytochrome *c* oxidase, citrate synthase, PDHC, the E1 subunit, LAD, and

α -ketoglutarate dehydrogenase complex were determined according to previously described methods.^{7,8} In sonicated fibroblasts, the activities of PDHC, LAD, and α -ketoglutarate dehydrogenase complex were determined as previously described.^{9,10}

Dichloroacetic acid, succinic acid (Sigma Chemical Co., St. Louis, Mo.), and lipoic acid (Astra Pharma, Frankfurt, Germany) were converted to their sodium salt (pH 5.0 to 7.0) with sodium hydroxide. These drugs were administered orally after Ministry of Health approval and informed parental consent.

RESULTS

Mean plasma lactate concentrations were significantly lower after therapy (2.4 ± 0.9 mmol/L) than before (4.8 ± 2.1 mmol/L) (Figure).

On admission, urinary organic acid analysis revealed elevated lactic, β -hydroxybutyric, α -ketoglutaric, and α -ketoadipic acid levels (11.63, 1.47, 4.14, and 0.27 mol/mol creatinine, respectively). After introduction of therapy, only mild organic aciduria was found (0.18, 0.04, 0.94, and 0.15 mol/mol creatinine, respectively).

In muscle, PDHC activity was 0.51 mU/gm wet weight, LAD 11.0 mU/gm, and α -ketoglutarate dehydrogenase complex 0.54 mU/gm (control values, 5.0 ± 1.8 , 101 ± 26 , and 3.8 ± 1.2 mU/gm, respectively). The activities of the other enzymes were within the normal range. In fibroblasts, the activity of PDHC was 14.1 nmol/hr per milligram of protein, LAD 235 nmol/hr per milligram, and α -ketoglutarate dehydrogenase complex 14.4 nmo/hr per milligram (control values, 23.4 ± 3.0 , 2334 ± 288 , and 22.2 ± 4.8 nmol/hr per milligram of protein, respectively).

DISCUSSION

Lipoamide dehydrogenase is one of the three catalytic proteins of the PDHC that converts pyruvate to acetyl-coenzyme A. LAD is also a component of two other α -keto acid dehydrogenase complexes: α -ketoglutarate dehydrogenase complex and branched-chain keto acid dehydrogenase complex. Thus a deficiency of LAD results in extensive metabolic disturbances, including lactic acidemia, Krebs cycle dysfunction with decreased NADH production, and impaired degradation of branched-chain amino acids.

Five patients with LAD deficiency have been reported.¹⁻⁵ All had severe neurologic damage early in life. Their clinical course was characterized by frequent episodes of metabolic decompensation and slow neurologic deterioration. Therapy with thiamine, glutamine, biotin, lipoic acid, restriction of branched-chain amino acids, and a low-carbohydrate, high-fat diet did not seem to influence their neurologic course; only lipoic acid was reported to be of some biochemical benefit. Three patients died at 7 to 21 months of age, and two remained severely retarded.

For the past 3 years our patient has been treated with DCA, thiamine, and carnitine. During this period the frequency and severity of his decompensation episodes decreased markedly, and his plasma lactate concentration was maintained at nearly normal levels. No adverse effects of this therapy have been observed, and at 5 years of age his cognitive functions were age appropriate, whereas his motor development was moderately impaired. The reason for this favorable outcome is unclear. DCA is effective in lowering plasma lactate levels, but its administration has not been associated with improvement of preexisting neurologic damage.¹¹ Our patient had only mild neurologic impairment when therapy was initiated. In view of the normal level of cerebrospinal fluid lactate and the normal results on neuroimaging and neurophysiologic studies, the possibility of a high residual LAD activity in the central nervous system cannot be excluded. We speculate that the main contribution of this therapy was preventive, by reducing the frequency and severity of the decompensation episodes. In previously described patients with LAD deficiency, such events worsened preexisting neurologic damage.^{4,5}

We conclude that DCA administration may be of benefit in children with LAD deficiency for the control of plasma lactate values and the attenuation of frequency and severity of decompensation episodes.

We acknowledge most helpful discussions with Prof. C. Bachmann, Switzerland, and the expert technical assistance of E. Chen.

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