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Glutaric Acidemia Type II: Neuroimaging and Spectroscopy Evidence for Developmental Encephalomyopathy

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Glutaric acidemia type II is associated with neonatal hypoketotic hypoglycemia, metabolic acidosis, profound hypotonia, progressive cardiomyopathy, and early death. Deficiency of either electron transfer flavoprotein or electron transport flavoprotein:ubiquinone oxidoreductase leads to intramitochondrial accumulation of metabolites of compounds oxidized by enzymes that transfer electrons to flavoprotein. No detailed results of antemortem neuroimaging or magnetic resonance spectroscopy have been described previously. We investigated a patient with typical neonatal onset glutaric acidemia type II without obvious dysmorphogenesis or renal malformations. Cranial tomographic scan revealed hypoplastic temporal lobes and marked widening of the sylvian fissures ("bat-wing" appearance). Cranial magnetic resonance imaging documented underdeveloped frontal and temporal lobes with delayed myelination and hypoplasia of the corpus callosum. ^{31}P-Magnetic resonance spectroscopy of muscle was grossly abnormal with a very low energy state consistent with mitochondrial dysfunction. ^{1}H-Magnetic resonance spectroscopy of brain revealed elevated intracerebral lactate concentration and abnormally high choline/creatine ratio suggestive of dysmyelination. These findings constitute the first in vivo evidence of a developmental encephalomyopathy in glutaric acidemia type II.

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Introduction

Glutaric acidemia type II (multiple acyl-coenzyme A dehydrogenase deficiency) or GA II is an autosomal recessive inborn error of fatty acid and amino acid metabolism [1] first described in 1976 [2]. It results from impaired flavin-mediated transfer of electrons between mitochondrial matrix dehydrogenases and the electron transport chain due to either defective electron transfer flavoprotein (ETF) or ETF:ubiquinone oxidoreductase (ETF:QO) [3]. Biochemically it is characterized by profound nonketotic hypoglycemia, metabolic acidosis, and organic (dicarboxylic) aciduria featuring variable combinations of organic acids including short chain volatile acids (isovaleric, isobutyric, 2-methylbutyric), glutaric, ethylmalonic, 3-hydroxyisovaleric, 2-hydroxyglutaric, 5-hydroxyhexanoic, adipic, suberic, sebacic, and dodecanedioic acids [4].

Several distinctive clinical phenotypes of GA II have been recognized [1]. One phenotype is a neonatal onset variant with congenital anomalies which features the early onset (24-48 hours of age) of severe hypoglycemia, metabolic acidosis, hypotonia, hepatomegaly, and renal cysts arising in a dysmorphic child with death occurring within the first week [5]. A second phenotype is a neonatal onset variant without congenital anomalies. These children are nondysmorphic, have severe early onset metabolic disturbances, and develop a progressive cardiomyopathy that results in death by age 1 year [6]. The final phenotype is a later onset variant characterized by episodic metabolic

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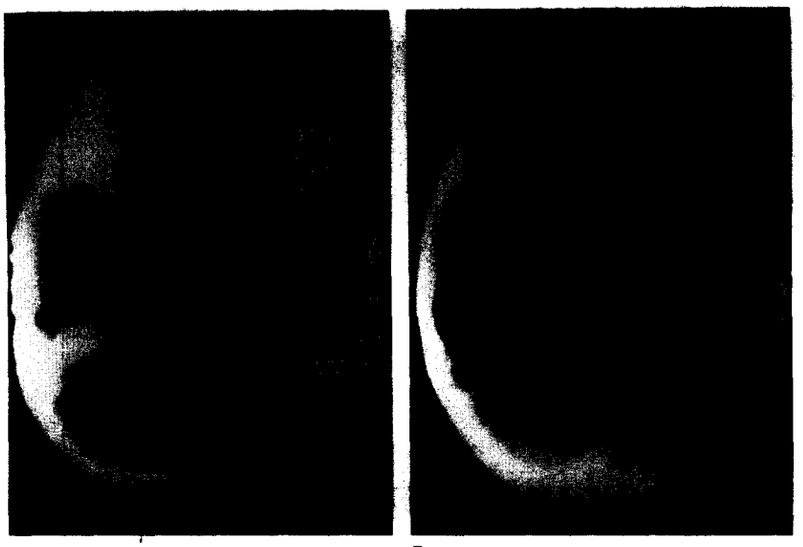

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Figure 1A, B. Axial CT scans with contrast medium demonstrate bilateral hypoplastic temporal lobes with near symmetrical increased CSF volume anterior in the temporal fossae. There is some prominence of the basal cisterns.

derangements in infancy, childhood, or adulthood associated with either progressive myopathy [7,8] or an extrapyramidal movement disorder [6].

The limited information that exists concerning central nervous system effects of GA II from antemortem neuroimaging studies or pathologic examination at autopsy documents focal cortical dysplasia and abnormal neuronal migration in early onset cases [9], and selective basal ganglia involvement in later onset patients with an extrapyramidal syndrome [6].

We present a patient with typical early onset GA II investigated prior to death when metabolically stable with complementary neuroimaging and magnetic resonance spectroscopy studies which document an underlying developmental encephalomyopathy.

Case Report

The patient, a native Indian (Mohawk) male, was the product of the fourth pregnancy of his mother. His parents were fourth cousins. Her first child, by a different father, was a normal girl. The second, a boy, was diagnosed at 3 months of age as having glutaric acidemia type II (elevated glutaric acid, 2-hydroxyglutaric acid, ethylmalonic acid, isovalerylglycine, and hexonylglycine) and died at the age of 5 months. The third pregnancy ended in a therapeutic abortion precipitated by prenatal analysis of amniotic fluid metabolites indicating the presence of glutaric acid in the amniotic fluid consistent with a diagnosis of glutaric acidemia type II.

The pregnancy was uneventful except for first trimester bleeding. Amniocentesis was not performed at the parents' request. Delivery was via cesarean section at 39 weeks gestation, birth weight was 3,790 gm, and Apgar score was 9 at 5 min. There were no neonatal complications and the infant was discharged at 3 days of age.

Urinary organic acid screening at 1 day of age documented elevation of glutaric acid and other even-chain dicarboxylic acids.

Initial neurologic assessment at 7 weeks of age documented borderline macrocephaly, prominent hepatomegaly, and a palpable spleen tip. Prominent head lag and truncal hypotonia were evident. Developmentally the child smiled responsively, fixed and followed, and transiently attempted to lift his head in the prone position. Dysmorphic features were absent.

Riboflavin and carnitine supplementation was initiated and the infant

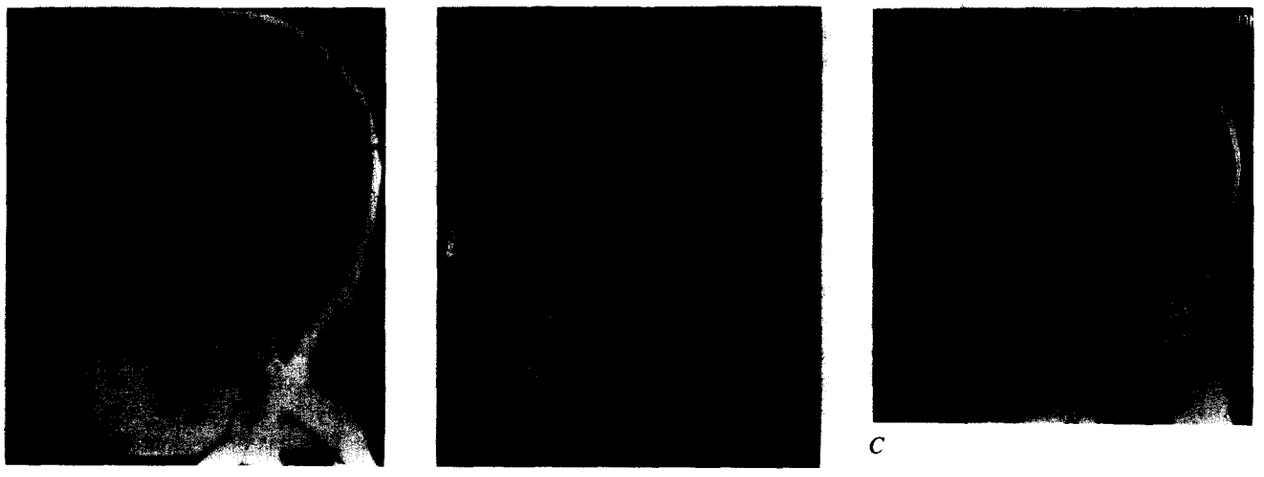

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Figure 2. (A) Sagittal T_1-weighted image displays a small temporal lobe with increased CSF space anteriorly. TR: 550 ms, TE: 19 ms. (B) Axial T_2-weighted image displays hypoplastic temporal lobes with increased CSF volume anterior to the temporal lobes. TR: 2,100 ms, TE: 78 ms. (C) Midline sagittal T_1-weighted image displays uniform hypoplasia of the corpus callosum, slight ventricular enlargement, and prominence of CSF spaces. TR: 550 ms, TE: 19 ms.

was admitted at 14 weeks of age for investigation, including cranial computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS). Chest x-ray and abdominal ultrasound were normal without evidence of renal malformations and an electrocardiogram documented significant ST segment changes. Echocardiogram documented reduced left ventricular ejection fraction (36%).

Carnitine and riboflavin supplementation was continued and the infant was readmitted 2 weeks later with pronounced vomiting. The parents requested palliative measures only and the infant died at 4 months of age. Permission for postmortem examination was refused.

Neuroimaging Studies

Neuroimaging studies (Figs 1, 2) demonstrated bilateral hypoplastic temporal lobe with symmetric increased cerebral spinal fluid (CSF) volumes anteriorly in the temporal fossae. The basal cisterns were widened with a slightly enlarged ventricular system. The corpus callosum was uniformly thin.

Proton and phosphorus magnetic resonance spectroscopy studies were performed using a 1.5 T combined imaging and spectroscopy system (Philips Medical Systems, The Hague, The Netherlands).

^{1}H-Spectroscopy of Brain. Proton spectrum of brain was obtained as previously described [10] from a supraventricular volume of interest (VOI) containing some gray but mostly white matter, measuring 78 mm anteroposterior × 56 mm left-right × 18 mm craniocaudal and positioned superior to the lateral ventricles, parallel to the horizontal plane.

The brain spectroscopy data (Fig 3) were compared to values from pediatric controls [11] expressed as mean ± S.D. The relative signal intensity of *N*-acetyl aspartate (NAA)/creatine was 2.0, which is low but within the normal range for age. Thus significant neuronal damage could not be demonstrated at the time of MRS examination. The choline/creatine relative resonance intensity was markedly elevated at 2.3, suggesting some active or recent demyelination or dysmyelination [10]. Moderately elevated lactate (lactate/creatine of 0.38) in central white matter, on the order of 3 times normal, was demonstrated. This confirms the presence of abnormal oxidative metabolism centrally.

^{31}P-Spectroscopy of Muscle. Muscle spectra (Fig 4) were obtained using a 6-cm surface coil positioned beneath the resting gastrocnemius as previously described [12]. Informed consent was obtained.

Limited normative data for muscle spectra exist for infants. Inorganic phosphate concentration was significantly elevated at 7.9 mmol/L (controls, mean ± S.D.: 4.0 ± 0.8), with a very low phosphorylation potential of 9 L/mol (151 ± 40). Phosphocreatine concentration was significantly reduced at 18.5 mmol/L (32.4 ± 1.8) and ADP concentration significantly elevated at 105 μmol/L (17.7 ± 4.0). These findings suggest an extremely low energy state of phosphate-containing metabolites consistent with significant mitochondrial dysfunction.

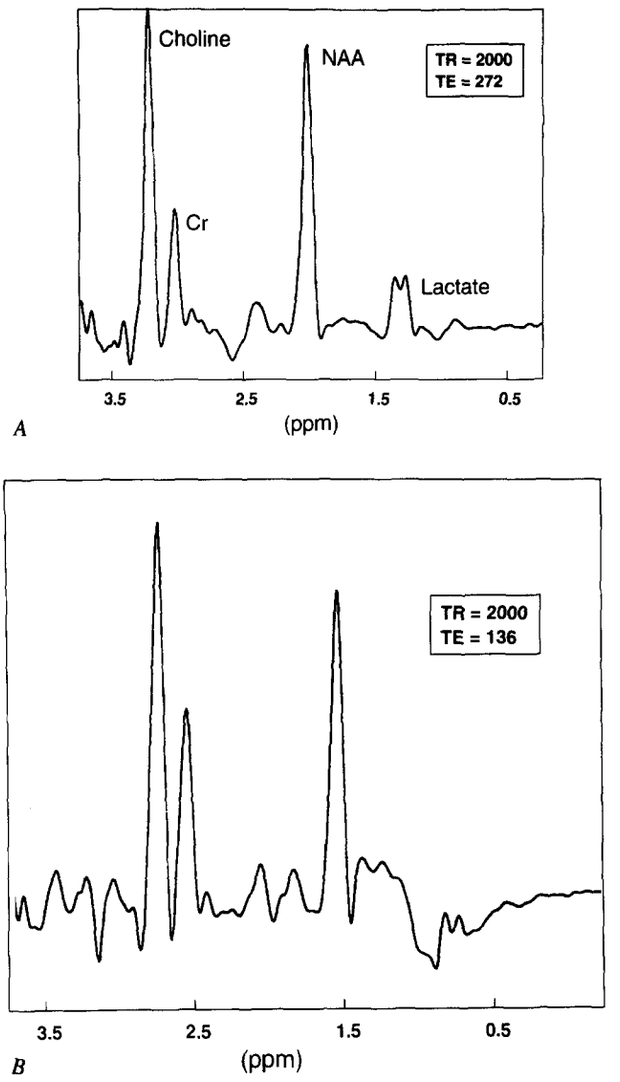

Figure 3A, B. ^{1}H-Magnetic resonance spectroscopy of brain of patient using TR and TE parameters as indicated. Cr = creatine; ppm = parts per million; NAA = N-acetyl aspartate.

Discussion

The characteristic urinary organic acid excretion pattern together with fibroblast studies on a previously affected sibling established the diagnosis of GA II in our patient. Since the original description of this entity [2], genetic and phenotypic heterogeneity has been apparent [1] with varying disease resulting presumably from several different mutant alleles at the ETF;QO, ETF-α, and ETF-β loci [13,14]. Involvement of the neuraxis at various levels underlies some of the major clinical manifestations of this disorder. Postmortem pathologic investigations have documented focal cortical dysplasias and heterotopias [9] suggestive of an in utero onset dysplastic process. In addition, encephalomalacia with gliosis [4] and basal ganglia neuronal loss with gliosis has been described [6].

Neuroimaging in our patient suggests a dysplastic process beginning in utero featuring abnormalities of neuronal proliferation and migration with a predilection for the temporal lobes with concomitant hypomyelination of the corpus callosum. This pattern of cerebral dysplasia and callosal hypoplasia is nonspecific and has been observed in other metabolic disorders [15,16], reflecting a possible common disturbance in energy metabolism or the accumulation of toxic intermediates. The CT appearance of our patient with GA II is identical to the appearance described for GA I [16]. This similarity is distinctive in the nearly identical "bat-wing" appearance of the temporal areas in both conditions. It has been cautioned that the temporal increased CSF spaces may be erroneously attributed to external hydrocephalus. This has been identified as a potential diagnostic "pitfall" [16].

Magnetic resonance spectroscopy provides a noninvasive technique that allows for direct observation of certain metabolites in brain or muscle. In our patient, proton MRS revealed the presence of lactate in the brain, which is an

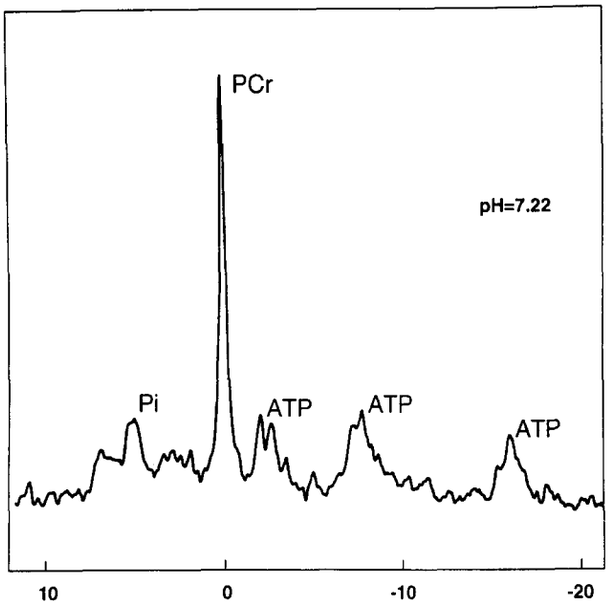

Figure 4. ^{31}P-Magnetic resonance spectroscopy of muscle of patient. PCr = phosphocreatine; Pi = inorganic phosphate; ATP = adenosine triphosphate.

indirect index of impairment of cerebral oxidative metabolism. The abnormally high choline/creatine ratio suggested some element of dysmyelination. Significant neuronal damage could not be demonstrated since the NAA/creatine ratio was low normal. Phosphorus MRS of muscle in our patient was grossly abnormal with an extremely low energy state of phosphate-containing metabolites consistent with significant mitochondrial dysfunction. Thus spectroscopic studies document on-going abnormalities in oxidative metabolism both centrally and peripherally with associated functional abnormalities in myelination. From a clinical perspective, the prominent hypotonia manifested by early-onset patients has both a central and neuromuscular cause.

Neuroimaging and MRS provide complementary noninvasive antemortem information regarding the neurologic extent of metabolic derangement. These studies permit the conceptualization of GA II as a developmental encephalomyopathy featuring secondary impairment of the energy intensive processes of neuronal proliferation and migration as well as myelination as a result of the uncoupling of cellular oxidative phosphorylation. This uncoupling occurs presumably as a consequence of the accumulation of short chain fatty acids [17] that is a by-product of the impaired flavin-mediated electron transfer [3]. Within this conceptual framework, phenotypic heterogeneity is likely to be the result of variations in the degree and regional distribution of actual mitochondrial dysfunction.

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