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Glutaric Aciduria Type I: A Common Cause of Episodic Encephalopathy and Spastic Paralysis in the Amish of Lancaster County, Pennsylvania

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We have diagnosed type I glutaric aciduria (GA-I) in 14 children from 7 Old Order Amish families in Lancaster County, Pennsylvania. An otherwise rare disorder, GA-I appears to be a common cause of acute encephalopathy and cerebral palsy among the Amish. The natural history of the disease, which was previously unrecognized in this population, is remarkably variable and ranges from acute infantile encephalopathy and sudden death to static extrapyramidal cerebral palsy to normal adult. Ten patients first manifested the disease between 3 and 18 months at the time of an acute infectious illness. Four of these children died in early childhood, also during acute illnesses. However, there has been little progression of the neurological disease after age 5 years in the surviving children and intellect usually has been preserved, even in children with severe spastic paralysis.

When well, patients have plasma glutaric acid concentrations ranging from 4.8 to 14.2 μmol/liter (nl 0–5.6 μmol/liter) and urinary glutaric acid concentrations from 12.5 to 196 mg/g creatinine (nl 0.5–8.4 mg/g creatinine). We have found that GA-I can be diagnosed in the Amish by measurement of urinary glutaric acid concentrations using isotope-dilution gas chromatography/mass spectrometry, whereas the diagnosis can easily be missed by routine urine organic acid gas chromatography. Based on our observations about the natural history of GA-I in the Amish, we anticipate that, with early diagnosis afforded by GC/MS screening of individuals at risk, the combination of restriction of dietary protein and limitation of protein catabolism, dehydration, and acidosis during illnesses will prevent the onset or progression of neurological disease in Amish patients with this variant of GA-I.

KEY WORDS: glutaric acid, metabolic encephalopathy, cerebral palsy, Amish, organic aciduria, glutaryl coenzyme A dehydrogenase, movement disorders

INTRODUCTION

Type I glutaric aciduria type (GA-I, McKusick 23167) is an autosomal recessive inborn error of the metabolism of the amino acids lysine, hydroxylysine, and tryptophan caused by a deficiency of the mitochondrial enzyme, glutaryl-CoA dehydrogenase. The disorder has a variety of clinical presentations, from lethal hypoglycemic, ketoacidotic crisis to otherwise benign extrapyramidal cerebral palsy to normal adult [Goodman et al., 1975; Gregersen et al., 1977; Christensen et al., 1978; Leibel et al., 1980; Whelan et al., 1980; Dunger and Snodgrass, 1984; Bennett et al., 1986; Booth et al., 1988; Amir et al., 1989; Goodman and Frerman, 1989]. Typically, metabolic crises in GA-I are episodic and have a predilection for injuring the neostriatum, causing a spastic paralysis similar to that caused by birth asphyxia. We have recently discovered that GA-I is prevalent among the Old Order Amish of Lancaster County, Pennsylvania, a genetic isolate whose large burden of autosomal recessive diseases has already been the subject of extensive genetic study [McKusick, 1978]. Our experience with GA-I in the Old Order Amish has provided us with an unusual opportunity to study the disparate clinical courses and episodic intoxication associated with this prototypic disorder of organic acid metabolism.

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METHODS

Patient Ascertainment and Pedigree Analysis

Following diagnosis of the index case (XII-1), other cases were identified by organic analysis of random urine samples from children suspected by the parents of the index case or other members of the Amish community to have the same disorder or similar neurological problems. The genetic lineages of the sibships (Fig. 1) were established by reference to 2 genealogies privately published by the Amish community [Gingerich and Kreider, 1978; Beiler, 1988].

Urine Organic Acid Analysis

Urinary organic acid identification and quantification was performed by gas chromatography/mass spectrometry (GC/MS) as described previously [Kelley and Morton, 1988]. The concentration of glutaric acid in urine and plasma was determined by isotope-dilution GC/MS using a modification of the method of Ng et al. [1983]. Tetradeuterated glutaric acid (pentanedioic-2,2,4,4-d_4 acid; MSD Isotopes, Ltd., Montreal) was added to specimens to a concentration of 20 mg/g creatinine for urine and 20 μmol/liter for plasma. For plasma specimens only, 200 μl aliquots were mixed with saturated sodium borate solution (2.5 volumes), extracted once with 1 ml hexane to remove lipids, and thereafter treated the same manner as the urine specimens. The urine and plasma specimens were then titrated to pH 11–12 with 4 N NaOH and incubated at 80°C for 30 min to hydrolyze carnitine and glucuronic esters of glutaric acid and thereby allow measurement of total glutaric acid concentrations. After incubation, the samples were acidified to pH less than 1 with 100 μl of concentrated HCl and organic acids extracted with 1 ml ethyl acetate. An aliquot of the organic phase was dried under nitrogen at room temperature, dissolved in 50 μl of acetonitrile, and then incubated with 75 μl bis(trimethylsilyl)trifluoroacetamide with 1% trimethylchlorosilane (Pierce, Rockford, IL) for 30 min at 80°C. Gas chromatography of the trimethylsilyl derivatives was performed on a 0.2 mm × 25 m × 0.25 μ bonded-phase methylsilicone capillary column (Hewlett-Packard Ultra 1) programmed from 110 to 160°C at 4°C/min, then 30°C/min to 290°C for 15 min in a Hewlett-Packard 5890A gas chromatograph interfaced with a Hewlett-Packard 5970B mass selective detector. Mass spectral data from 12–13 min at m/z = 261 (glutaric acid) and m/z = 265 (glutaric acid-d_4) were collected and the peak areas integrated using the Hewlett-Packard GC/MS version 3.1.1 Pascal workstation.

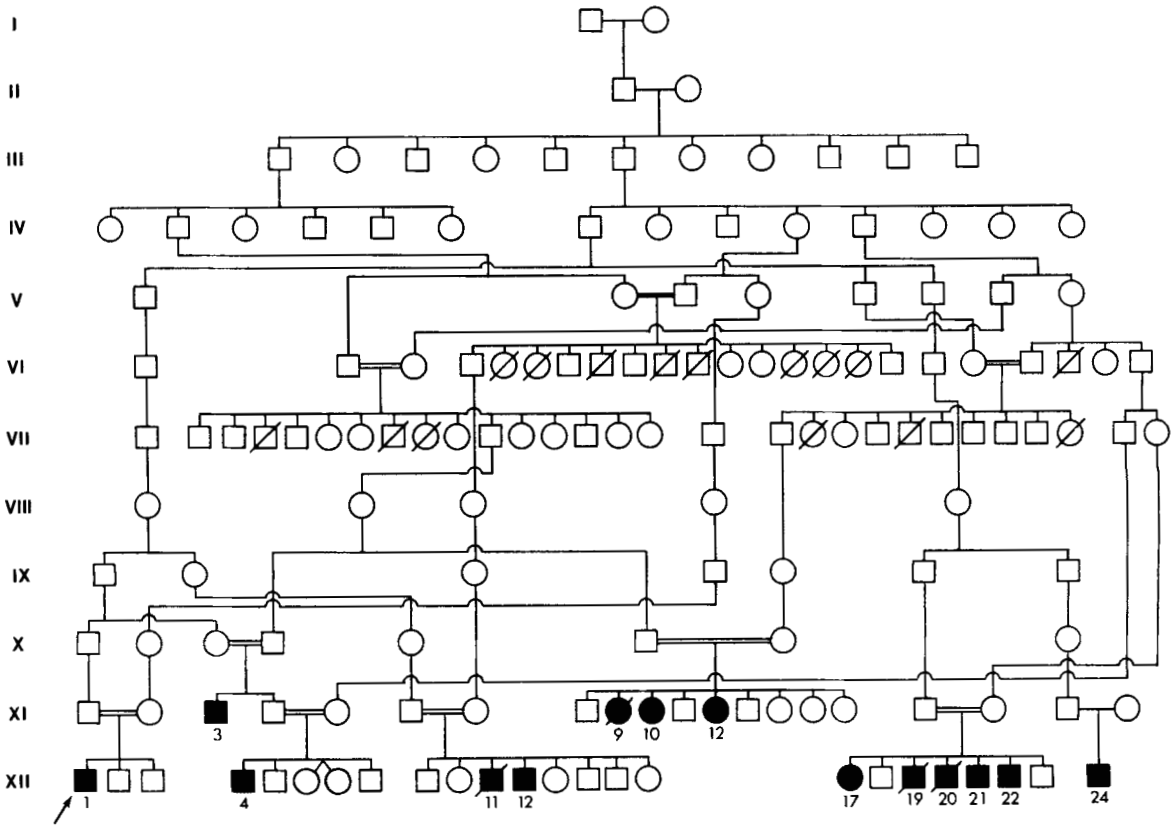

Fig. 1. Genealogy of type I glutaric aciduria in the Lancaster County, Pennsylvania, Old Order Amish. All but one parent (XI - 20) of the known cases are known descendents of John Lapp and his wife (I-1 and I-2). Cases marked with "/" in generations VI and VII are children of consanguineous matings who died in infancy or early childhood and who were called "special children" in the family records, as are the currently living patients with glutaric aciduria.

Enzymatic Analysis

Glutaryl coenzyme-A dehydrogenase activity was measured in mitogen-transformed peripheral lymphocytes as described previously [Booth et al., 1989].

CLINICAL REPORTS

Patient 1 (XII-1)

DL, the propositus, was the first child of healthy parents who were distantly related to a common ancestor (II-1). The child was normal at birth and was breast fed for the first year, during which time growth and development were normal. At age 14 months, on the third day of a mild gastroenteritis, he lost head control and the ability to stand or sit over a 12-hr period. Upon hospitalization, he was reported to be well-hydrated and had normal vital signs except for a respiratory rate of 60. He was an alert, responsive, but mute infant who was unable to suck or swallow and had almost no head control. His muscles were normally developed but tone was profoundly decreased. Deep tendon reflexes were difficult to obtain and Babinski reflexes were absent. The only significant laboratory abnormalities were a serum bicarbonate of 15 mEq/liter (nl 20–24 mEq/liter) and moderate ketonuria. Except for persistent hypotonia, he recovered almost completely over a 48-hr period while receiving intravenous glucose and saline. However, a similar episode of illness and neurological deterioration at age 18 months left him with residual choreoathetosis and spastic quadriparesis. At the time of the second illness, computerized tomography and magnetic resonance imaging of the head were interpreted as normal as was urine metabolic screening, including paper chromatography of amino acids and organic acids.

At age 5½ years, elective diagnostic testing for a possible inborn error of metabolism showed increased blood levels of pyruvate (0.15, 0.22 mmol/liter; nl 0.03–0.08 mmol/liter) and lactate (3.1, 3.7, 3.2 mmol/liter; nl 0.5–2.2 mmol/liter). Although, once again, a metabolic screen of the urine was reported as normal, gas chromatography of organic acids in the same urine specimen requested at a later time showed a diagnostically increased level of glutaric acid of 136 mg/g creatinine (nl < 11 mg/g creatinine). A simultaneous plasma glutaric acid level measured by isotope-dilution GC/MS also was increased to 11.2 μmol/liter (nl < 4.2 μmol/liter). The additional finding of increased amounts of 3-hydroxyglutaric acid in the urine was interpreted as consistent with the diagnosis of GA-I [Goodman and Frerman, 1989]. Although treatment with dietary protein restriction (1–1.5 g/kg per day) and riboflavin (100 mg BID) have been associated with a moderate reduction in urinary glutaric acid concentrations and subjectively decreased severity of choreoathetosis and spasticity, urinary glutaric acid levels have exceeded 1000 mg/g creatinine during 2 recent febrile illnesses.

Patient 2 (XI-3)

This 28-year-old man was normal until age 3 months when, after a period of irritability and poor feeding on day 7 of a varicella infection, he experienced an acute, afebrile episode of tonic posturing and thereafter became flaccid and unresponsive. Upon admission to a local hospital, he was found to have profound hypotonia and intermittent "stiffening" of the back and limbs. Results of laboratory tests, including blood glucose, electrolytes, and calcium and cerebrospinal fluid analysis, were normal. After recovery from the acute episode, which was diagnosed as varicella encephalitis, he was left with a residual spastic diplegia, partial bulbar palsy, and choreoathetosis. GA-I was diagnosed at age 28 years based on a urinary glutaric acid level of 166 mg/g creatinine. Despite spastic diplegia and moderate choreoathetosis, he has normal intelligence and regularly works in a carriage and harness repair shop. There has been no apparent progression of his neurological disease in the 27 years since the single damaging illness at age 3 months.

Patient 4 (XI-10)

RA was normal until age 11 months when she developed afebrile generalized tonic seizures on day 3 of a varicella infection. At the time of admission to a hospital, her blood levels of glucose, electrolytes, and ammonia were normal and her urinalysis remarkable only for moderate ketonuria. The cerebrospinal fluid glucose, protein, and cell counts also were normal. After recovery from the acute illness, she was left with total body spastic paralysis, which, despite the normal cerebrospinal fluid results, was attributed to varicella encephalitis. A CT scan of the brain at 15 years showed decreased density in the caudate and putamen bilaterally.

During a recent infectious illness, the concentration of glutaric acid in her urine increased from a baseline of 25 mg/g creatinine to greater than 5,000 mg/g creatinine. At the same time, the level of glutaric acid in plasma increased only slightly from a baseline of 7.2 μmol/liter to a maximum of 11.4 μmol/liter, indicating rapid clearance. Blood pH and levels of glucose and ammonia remained normal and no neurological changes occurred.

Patient 5 (XI-12)

KA was 12 years old when she was found to have a GA-I during routine testing of her family after her clinically affected sister (XI-9) was found to have GA-I. Although, in retrospect, her parents believe that her gross motor development was mildly delayed compared to her biochemically unaffected sibs, her intelligence is normal and her physical examination notable only for a head circumference at the 95th centile for age. In particular, speech, fine motor skills, muscle mass, muscle tone, and reflexes are normal.

Patient 10 (XII-19)

SyM was normal at birth and psychomotor development was appropriate for the first 6 months. He remained healthy until 6½ months when he developed a high fever, irritability, and poor feeding during the morning of the first day of an upper respiratory tract illness. By noon of the same day he had become lethargic and weak, and by mid-afternoon he had developed opisthotonic posturing. Shortly after admission to a local hospital, he had 2 generalized tonic seizures which lasted 1–2 min each. Serum chemistries were normal

except for a bicarbonate of 19 mEq/liter. The CSF cell count and glucose concentration were normal and bacterial culture sterile.

After resolution of the acute illness, SyM was left with global choreoathetoid spastic paralysis. An extensive evaluation at age 11 months, including urine metabolic screening and plasma amino acid quantification, was nondiagnostic. CT of his disproportionately enlarged head showed dilated subarachnoid spaces, typical of GA-I, but was otherwise unremarkable. After the acute injury, SyM failed to thrive and demonstrated no further motor development. He died suddenly at 2½ years. Because of SyM's normal development to 6 months, acute onset of choreoathetoid spastic paralysis and diagnosis of GA-I in 4 sibs, it is likely that his primary diagnosis also was GA-I.

Patient 12 (XII-21)

SM, the brother of patient 10, was normal from birth to 8 weeks of age when he was hospitalized because of fever and irritability. Although serum chemistries and cerebrospinal fluid analysis were normal, his discharge diagnosis was "viral encephalitis." In the 10 years following this acute illness, he has suffered from dysphagia, poor weight gain, and delayed gross motor development, but he has had no additional episodes of severe illness or further deterioration in his neurological condition.

GA-I was diagnosed at 11 years, based on a urinary glutaric acid concentration of 778 mg/g creatinine and nondetectable glutaryl coenzyme-A dehydrogenase activity in cultured lymphocytes. His most recent examination at 11 years was remarkable for a head circumference of 57 cm (95th centile), a dystonic smile, dysarthria, mild dysphagia, and mild choreoathetosis of the upper limbs. His gait was remarkable only for intoeing of the right foot. He walks several miles each day to school and runs without difficulty. He attends a regular Amish school and reads and comprehends normally.

Patient 14 (XII-24)

ME was noted by his parents to have poor head control and generally decreased muscle tone from early infancy, but he was otherwise considered to be normal. At age 6 months he developed an upper respiratory tract infection and fever, became extremely irritable, and rapidly lost the ability to nurse on day 3 of the illness. He was admitted to a hospital on the same day following several episodes of tonic stiffening, which were thought to be seizures. He was noted on physical examination to have normal vital signs and a head circumference at the 95th centile. He was alert but unable to suck and swallow, extremely hypotonic, and periodically opisthotonic. Laboratory studies were remarkable only for a venous pH of 7.36, pCO_2 of 28 mm Hg, and bicarbonate of 16 mEq/liter. After the possibility of GA-I was suggested by the grandparents, who read of the disorder in an Amish community newsletter, GA-I was diagnosed by gas chromatography, which showed urinary concentrations of glutaric acid greater than 3000 mg/g creatinine and of 3-OH-glutaric acid of 18 mg/g creatinine (nl $<$ 1 mg/g creatinine)

After diagnosis, the patient was treated with a protein-restricted diet (1–1.5 g/kg/day), Poly-Citra (2 ml/kg/day), and riboflavin (50 mg BID). Three days after the therapy was started the urinary glutaric acid concentration fell to 166 mg/g creatinine, but without clinical changes. However, after 3 additional weeks of therapy, the urinary glutaric acid level had decreased to 37 mg/g creatinine and marked clinical improvement had occurred. His suck, swallow, and character of cry had returned to normal, he could lift and hold his head while on his stomach, and he could once again sit with support. Although muscle tone in the limbs and deep tendon reflexes had returned to normal, intermittent choreoathetosis of the hands persisted.

RESULTS

Clinical Studies

Table I summarizes the clinical findings of 10 patients proven to have GA-I and 4 sibs presumed to have died of GA-I. Although we cannot be absolutely certain about the diagnosis of GA-I in the 4 patients who died before identification of the disease in the Amish, all 4 presumptive diagnoses were made in children with clinical histories and neurological findings very similar to those of a sib shown by organic acid analysis to have GA-I.

All patients, who range in age from 7 months to 28 years, were normal at birth and all but 2 appeared to develop normally for at least several months. The age of onset of neurological disease varied from 2 to 36 months and coincided with an infectious illness in 11 of the 14 patients. Seizures occurred in 4 of the 14 patients at the time of an acute illness and ultimately were associated with severe spastic paralysis in 3 of the 4. The clinical course of 2 patients in whom the onset of disease was gradual was characterized by hypotonia, delayed development of gross motor skills, irritability, and poor weight gain. One of these patients (Patient 9) is now 9 years old and has spastic diplegia and choreoathetosis. The other patient (Patient 11) deteriorated rapidly during a respiratory illness, became severely disabled, and died later at age 6 years. Of the 14 affected children, 4 (28%) have died. Three of these children (Patients 8, 10, 11) were severely debilitated at the time of death, while the 4th child (Patient 3) was normal until age 3⁴/₁₂ years when she lost motor control during a gastroenteritis in the same manner as her sibs, but deteriorated further and died of aspiration.

Of the surviving 10 children, 4 are severely disabled. These 4 children are quadriplegic, have little or no ability to speak, but retain good receptive language skills and communicate with family and teachers through communication boards or complex eye movements. Patient 6, a 5-year-old boy who is paraplegic and has severe choreoathetosis, is reported to have an IQ of 140. Seven of 14 patients had choreoathetosis and 5 of the 14 had macrocephaly, a common unexplained finding in GA-I. Prior to the recognition of GA-I in the Amish, most of these children had been given the diagnosis of idiopathic cerebral palsy by medical or rehabilitative professionals. Although we have found a wide range of clinical presentations and residual neurological disease in GA-I of the Amish, it is likely that our initial ascertainment

TABLE I. Clinical Characteristics of Amish Patients With Glutaric Aciduria*

Case	Age at diagnosis (years)	Age at disease onset (months)	Clinical characteristics					Method of diagnosis
			Onset of disease	Spasticity	Choreo-athetosis	Dysarthria	Head circ (%)	
1 (XII-1)	5	14	Vomiting, diarrhea	Total body	+	Mute	90	GA
2 (XI-3)	28	2	Day 7 of varicella; seizures, hypotonia	Diplegia	+	Mild	40	GA
3 (XI-9)	Died (3)	36	Vomiting, fever, coma, aspiration	None	−	None	Unknown	Hx,SD
4 (XI-10)	15	11	Day 3 of varicella; seizures, hypotonia	Total body	−	Mute	60	GA
5 (XI-12)	12	NA	Mild gross motor developmental delay	None	−	None	>95	GA
6 (XII-4)	5	6	Fever	Diplegia	+	Moderate	50	GA
7 (XII-11)	19	15	URI	Total body	−	Mute	Unknown	Hx
8 (XII-12)	Died (7)	6	Failure to thrive	Total body	−	Mute	Unknown	Hx
9 (XII-17)	9	3	Failure to thrive	Diplegia	+	Severe	95	GA/Enz
10 (XII-19)	Died (2½)	5	Failure to thrive; rapid deterioration during URI	Total body	−	Mute	30	Hx, SD
11 (XII-20)	Died (6½)	6	Fever: hypotonia, intermittent hypertonic posturing and seizures	Total body	−	Mute	25	Hx,SD
12 (XII-21)	11	2	Fever: otitis media	Diplegia mild	+	Mild	95	GA/Enz
13 (XII-22)	3	18	Fever and diarrhea	Diplegia	+	Mute	60	GA/Enz
14 (XII-24)	7/12	6	URI	None	+	NA	95	GA

*Abbreviations: NA, not applicable; Hx, history; SD, sibling diagnosis; Enz, enzyme assay; URI, upper respiratory tract infection.

is biased toward patients with static encephalopathy and choreoathetosis. However, because case 5 illustrates that GA-I in the Amish is also compatible with normal growth and development, we may with more complete testing of the Amish population identify proportionately more individuals with GA-I who have minimal or no clinical disease.

Metabolic Studies and Genetics

As shown in Table II, glutaryl coenzyme-A dehydrogenase (GCAD) activity was undetectable in lymphocyte cultures from 3 sibs (patients 9, 12, 13) with GA-I. The parents of the children and 2 normal sibs had enzyme activities approximately ½ of the mean control value. Although the enzyme level measured in vitro under stringent conditions was undetectable, the generally lower excretion of glutaric acid and milder disease in Amish patients compared to many published cases suggests that some residual enzyme activity exists in vivo.

Table III lists the results of quantification of urinary glutaric acid concentrations by gas chromatography using flame ionization detection and by isotope-dilution GC/MSD using tetradeuterated glutaric acid as the internal standard. Concentrations of glutaric acid in the blood of patients when well ranged from 1.9 to 19.6 μmol/liter. At the time of encephalopathy at age 6 months, patient 14 had plasma and cerebrospinal fluid levels of glutaric acid of 19.4 μmol/liter (nl, 0–4.2, n = 20) and 18 μmol/liter (nl, 1.0–1.8, n = 5), respectively. No statistically significant differences were found between the urinary glutaric acid levels of normal infants and those of older controls.

The enzymatic studies and pedigree of GA-I in the Amish are consistent with autosomal recessive inheritance. The present day Lancaster County Old Order Amish are descendants of a small number of Swiss families who emigrated to the Lancaster area between 1727 and 1770. Because marriage outside the Old Order families is rare, this religious sect has been essentially a closed genetic population for more than 8 generations. All cases of glutaric aciduria we have identified are descendants of John Lapp (name of wife unknown) (1710–1795), who emigrated from Switzerland to the United States in the 1730s. Today, obligate carriers of the defect are widely distributed among the major family groups of the Old Order Amish, which also indicates that the gene was introduced into the population in an early generation. Moreover, because of the large number of cases identified in a short period of time without general screening, the gene frequency of the defect may

TABLE II. Glutaryl-CoA Dehydrogenase Activity in Cultured Lymphocytes

	Activity*	Percent control
Control (n = 4)	12.3	100
X-9 (Father)	6.4	51
X-10 (Mother)	4.0	33
XI-19	5.8	47
XI-22	5.9	48
XI-18	0	0
XI-21	0	0
XI-23	0	0

*Micromoles glutarate oxidized/hr/mg protein.

TABLE III. Urinary Glutaric Acid Excretion

	Urinary glutaric acid concentration		
	Number of samples	Mean ± SD mg/g creatinine	Range mg/g creatinine
Flame ionization detector			
Amish normal controls	48	4.6 ± 2.4	0–10.7
Amish with glutaric aciduria	38	244 ± 398	17–1735
Isotope-dilution mass spectrometry			
Amish normal controls	63	4.1 ± 1.7	0.5–8.4
Amish with glutaric aciduria[a]	15	61.9 ± 66.2	12.5–196

[a]Samples with the lowest glutaric acid concentrations were reanalyzed by the isotope ratio method. The 15 samples were from patients managed by protein restricted diets (1–1.5 g/kg-day), riboflavin (10 mg/kg-day), and who were clinically stable at the time the sample was obtained.

be as high as the 0.05 estimated for other common Amish recessive traits [McKusick, 1978]. While it is possible that some variability of GA-I in the Amish can be explained by segregation of more than one abnormal allele, a well-known aspect of Tay-Sachs disease in the Ashkenazi Jewish population [Triggs-Raine et al., 1990], the descent of all GA-I patients from a single immigrant Amish couple and the considerable intrasibship variability of the disorder suggests that GA-I in the Amish may indeed be genetically homogeneous.

DISCUSSION

The natural history of GA-I in the Lancaster County Amish, and in particular the extremely variable nature of the disease within sibships, illustrates well the diverse presentations of an episodic organic aciduria. Of particular importance is that the individual clinical courses of GA-I in Amish children indicate that neurological damage is largely caused by episodic intoxication of the brain by glutaric acid or a related metabolite during a susceptible early stage of brain development but not later in childhood. For example, patients 9, 12, and 13 are sibs who have undetectable glutaryl-CoA dehydrogenase activity in lymphocytes, yet they have followed very different clinical courses, possibly because they had their acute crises at different ages. Thus, the highly variable course of the GA-I in the Amish may be determined not only by the severity and frequency of acute episodes of illness but also by the specific age at which acute CNS injury occurs. Although we are not aware of an increased incidence of degenerative disorders of the basal ganglia in adult Amish, the possibility of such complications developing later in life should be considered. A further important corollary of these observations is that if metabolic decompensation and acute neurological intoxication at times of illness can be better understood and treated promptly, then neurological disease may be largely preventable. Indeed, all 4 infants whom we have identified through newborn screening since completion of our initial field studies and have followed closely at times of illness continue to develop normally (H. Morton, unpublished observations).

The fever and fasting that accompany simple childhood illnesses cause substantially increased catabolism of endogenous protein and, in patients who have GA-I, rapid accumulation of glutaric acid and its associated metabolites. In general, we have found 20- to 200-fold increases in urinary glutaric acid concentrations at the time of infections and fasting in our patients. Based on our experience with the Amish, we suspect that the ability to clear glutaric acid from the blood at times of illness may significantly influence outcome. For example, patient 14 sustained permanent neurological injury at the time of initial diagnosis when glutaric acid excretion exceeded 3000 mg/g creatinine and concentrations of glutaric acid in plasma and spinal fluid were increased 5- to 10-fold. In contrast, patient 3 at age 16 years had a severe wound infection associated with markedly increased glutaric acid concentrations in the urine but only a relatively small increase in the plasma glutaric acid level from a baseline of 7.2 μmol/liter to a maximum of 11.2 μmol/liter. During the illness, she showed no acidosis, hypoglycemia, or hyperammonemia, and no progression of neurological disease. Factors that limit the clearance of glutaric acid by the kidney, such as intravascular volume contraction and acidemia, may lead to the accumulation of toxic levels of glutaric acid in the blood and rapidly evolving neurological injury, as suggested also by the study of basal ganglial injury in methylmalonic aciduria [Heidenreich et al., 1988].

As shown in Table II, careful quantification of urinary glutaric acid concentrations appears to be an effective way to test individuals in the Amish population at risk for GA-I. Although secondary increases in urinary glutaric acid concentrations may be found in association with other metabolic disorders, such as multiple acyl-CoA dehydrogenase deficiency, medium chain acyl-CoA dehydrogenase deficiency, and propionic acidemia, these are readily distinguished from GA-I by the presence of other pathologic metabolites and by the usually increased levels of 3-OH-glutaric acid in GA-I [Goodman and Markey, 1981; Goodman and Frerman, 1984]. However, we have found that the excretion of 3-OH-glutaric acid, a metabolite considered essentially pathognomonic of GA-I, often is normal in our patients and therefore cannot be used for screening purposes. In contrast, the urinary glutaric acid level in our patients has been consistently diagnostic, even when, as Table II illustrates, the patients are well and under good dietary control. Although the assay of glutaryl-CoA dehydrogenase in white blood cells or fibroblasts can be done in selected cases, enzymatic studies are technically and economically impractical for testing the large number of infants and children within this Amish population who are at high risk for the disorder.

The diagnosis of GA-I in several symptomatic Amish children who had clinical findings suggestive of a metabolic disease was missed during extensive evaluations both at local hospitals and at major pediatric centers. The most common reasons for a missed diagnosis of GA-I among the Amish were (1) failure to consider or pursue

the diagnosis of a metabolic disorder because of unfamiliarity with metabolic disorders or the belief that metabolic disorders are both rare and untreatable, (2) the misconception that an organic acidemia is unlikely in the absence of metabolic acidosis, (3) the assumption that a normal "metabolic screen" rules out organic acid disorders, (4) failure of laboratories to establish normal concentration ranges for organic acids in urine or to recognize that the excretion of glutaric acid may be only slightly increased above normal levels when an affected child is metabolically stable. Today, GA-I is just one of a rapidly growing number of inborn errors of organic acid metabolism that can be missed if only the largest peaks in an organic acid chromatogram are analyzed or if only nonacute urine specimens are submitted for study.

Finally, it is important to note that many of the Amish children with spastic paralysis secondary to GA-I carried the diagnosis of idiopathic cerebral palsy prior to the recognition of GA-I. If our estimate of the frequency of GA-I in the Amish is correct, then this metabolic disorder is a major cause of "cerebral palsy" in the Lancaster County Amish. Although the Lancaster Amish population may be unusual in this respect, studies of the relationship between glutaric aciduria and cerebral palsy may ultimately prove to be of more general interest than first apparent. Very little is known about the cause of most cases of cerebral palsy in the general population, and although it is a commonly held belief that cerebral palsy is most often caused by hypoxic-ischemic damage to the fetal or neonatal brain from complications of pregnancy or delivery, the results of the National Collaborative Study of Cerebral Palsy indicate that this belief is unfounded [Nelson and Ellenberg, 1984, 1986]. Fewer than 13% of cases of cerebral palsy in the National Collaborative Study could be securely attributed to birth-related injury. An understanding of the biochemical basis of the neurological damage associated with glutaric aciduria and similar inborn errors of organic acid metabolism may provide new insights into biochemical causes and methods of prevention of spastic paralysis in the general population.

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REFERENCES

Amir N, Elpeleg ON, Shalev RS, Christensen E (1989): Glutaric aciduria type 1: Enzymatic and neuroradiologic investigations of two kindreds. J Pediatr 114:983–989.

Beiler K (1988): "Fisher Family History, Descendants and History of Christian Fisher (1757–1838)," 3rd ed. Gordonville, PA: Eby's Quality Printing.

Bennett MJ, Marlow N, Pollitt RJ, Wales JKH (1986): Glutaric aciduria type I biochemical and post mortem findings. Eur J Pediatr 145:403–404.

Booth FA, Chudley AE, Seargeant LE, Dilling L, Greenberg CE, Seshia SS, McClarty B, de Groot WG, Goodman SI, Haworth JC (1990): Manitoba variant of glutaric aciduria type 1. J Pediatr (in press).

Cahill GF (1970): Starvation in man. N Engl J Med 282:668–675.

Christensen E, Brandt NJ (1978): Studies on glutaryl-CoA dehydrogenase in leukocytes, fibroblasts, and amniotic fluid cells. The normal enzyme and the mutant form in patients with glutaric aciduria. Clin Chim Acta 88:267–278.

Dunger DB, Snodgrass GTAT (1984): Glutaric aciduria type 1 presenting with hypoglycemia. J Inher Metab Dis 7:122–124.

Gingerich HF, Kreider RW (1978): "Amish and Amish-Mennonite Genealogies." Gordonville, PA: Pequea Publishers.

Goodman SI, Frerman FE (1984): Glutaric aciduria Type II: Multiple acyl-CoA dehydrogenase deficiency. J Inher Metab Dis 7 (Suppl 1): 33–38.

Goodman SI, Frerman FE (1989): Organic acidemias due to defects in lysine oxidation. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): "The Metabolic Basis of Inherited Disease," 6th ed. New York: McGraw-Hill, pp 845–853.

Goodman SI, Markey SP (1981): "Diagnosis of Organic Acidemias by Gas Chromatography-Mass Spectrometry." New York: ALan R. Liss, pp 54–61.

Goodman SI, Markey SP, Moe PG, Miles BS, Teng CC (1975): Glutaric aciduria: A new disorder of amino acid metabolism. Biochem Med 12:12–21.

Gregerson N, Brandt, Christensen E, Gron I, Rasmussen K, Brandt S (1977). Glutaric aciduria: Clinical and laboratory findings in two brothers. J Pediatr 90:740–745.

Heidenreich R, Natowicz M, Hainline BE, Berman P, Kelley RI, Hillman RE, Berry GT (1988). Acute extrapyramidal syndrome in methylmalonic acidemia: "Metabolic" stroke involving the globus pallidus. J Pediatr 113:1022–1027.

Hostetler JH (1980): "Amish Society," 3rd ed. Baltimore, MD: The Johns Hopkins University Press, pp 319–322.

Kelley RI, Morton DH (1988): 3-Hydroxyoctanoic aciduria: Identification of a new organic acid in the urine of a patient with non-ketotic hypoglycemia. Clin Chim Acta 175:19–26.

Leibel RL, Shih VE, Goodman SI, Bauman ML, McCabe ERB, Zwerdling RG, Bergman I, Costello C (1980): Glutaric acidemia: A metabolic disorder causing progressive choreoathetosis. Neurology 30:1163–1168.

McKusick VA (1978): "Medical Genetic Studies of the Amish." Baltimore, MD: Johns Hopkins University Press.

Nelson KB, Ellenberg JH (1984): Obstetric complications as risk factors for cerebral palsy or seizure disorders. J Am Med Assoc 251:1843–1848.

Nelson KB, Ellenberg JH (1986): Antecedents of cerebral palsy: Multivariate analysis of risk. N Engl J Med 315:81–86.

Ng KJ, Andresen BD, Hilty MD, Bianchine JR (1983): Identification of long chain dicarboxylic acids in the serum of two patients with Reye's syndrome. J Chromatogr 276:1–10.

Triggs-Raine BL, Feigenbaum AJ, Natowicz M, Skomorowski M, Schuster SM, Clarke JTR, Mahuran DJ, Kolodny EH, Gravel RA (1989): Screening for carriers of Tay-Sachs disease among Ashkenazi Jews: A comparison of DNA-based and enzyme-based tests. N Engl J Med 323:6–12.

Whelan DT, Hill R, Ryan ED, Spate M (1980): L-Glutaric acidemia: Investigation of a patient and his family. Pediatrics 63:88–93.