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ARTICLE

Type I Glutaric Aciduria, Part 1: Natural History of 77 Patients

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Type I glutaric aciduria (GA1) results from mitochondrial matrix flavoprotein glutaryl-CoA dehydrogenase deficiency and is a cause of acute striatal necrosis in infancy. We present detailed clinical, neuroradiologic, molecular, biochemical, and functional data on 77 patients with GA1 representative of a 14-year clinical experience. Micrencephalic macrocephaly at birth is the earliest sign of GA1 and is associated with stretched bridging veins that can be a cause of subdural hematoma and acute retinal hemorrhage. Acute striatal necrosis during infancy is the principal cause of morbidity and mortality and leads to chronic oromotor, gastroesophageal, skeletal, and respiratory complications of dystonia. Injury to the putamen is heralded by abrupt-onset behavioral arrest. Tissue degeneration is stroke-like in pace, radiologic appearance, and irreversibilty. It is uniformly symmetric, regionally selective, confined to children under 18 months of age, and occurs almost always during an infectious illness. Our knowledge of disease mechanisms, though incomplete, is sufficient to allow a rational approach to management of encephalopathic crises. Screening of asymptomatic newborns with GA1 followed by thoughtful prospective care reduces the incidence of radiologically and clinically evident basal ganglia injury from approximately 90% to 35%. Uninjured children have good developmental outcomes and thrive within Amish and non-Amish communities.

KEY WORDS: type I glutaric aciduria; micrencephalic macrocephaly; basal ganglia injury

Time is that wherein there is opportunity, and opportunity is that wherein there is no great time. . . . Healing is a matter of time, but it is also a matter of opportunity.
—Hippocrates, *Epidemics*

INTRODUCTION

Type I glutaric aciduria (GA1) is a disorder of organic acid metabolism caused by mutations in the glutaryl CoA-dehydrogenase gene (GCDH) on chromosome 19p13.2. Glutaryl-CoA dehydrogenase is a homotetrameric flavin-dependent mitochondrial matrix enzyme that mediates oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA in the degradation pathway for lysine, hydryoxylysine, and tryptophan. The principal clinical manifestation of GA1 is acute focal striatal necrosis in infancy [Bennett et al., 1986; Kimura et al., 1994; Baric et al., 1998; Busquets et al., 2000; Goodman and Frerman, 2001]. Morton et al. [1991] first identified GA1 as the cause of familial "Amish cerebral palsy" among the conservative Plain sect in Lancaster County, Pennsylvania, and found that 82% of the first 17 retrospectively identified patients remained severely disabled by dystonia following abrupt neurological deterioration at ages ranging from 3 to 18 months, often in association with an infectious illness.

GA1 subsequently became a major focus of clinical research and patient care at the Clinic for Special Children (CSC), which now has experience with 77 patients over a 14-year period (1988–2002). These patients range in age from 2 weeks to 42 years and encompass a broad spectrum of phenotypic expression. Here, we present the natural history of GA1 of this large group of affected individuals from infancy to adulthood. Although work with GA1 initially focused upon the Amish population of Lancaster County, more than half of the patients in this study are non-Amish. Despite incomplete knowledge of disease mechanisms, early diagnosis and thoughtful care reduce neurological disability in this patient population. The clinical, neuroradiologic, and laboratory characteristics of the group allow us to construct a pathophysiologic model of acute striatal necrosis and generate key questions for future research. This model is presented fully in a companion paper [Strauss and Morton, 2003].

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PATIENTS AND METHODS

Seventy-seven patients (37 Amish, 40 non-Amish) ranging from birth to 44 years reflect a 14-year clinical experience from 1988–2002. The majority of patients were studied prospectively. Detailed clinical observations were supplemented with extensive biochemical testing. Over 80 magnetic resonance imaging (MRI) studies utilizing T1, T2, diffusion-weighted imaging (DWI), and fluid-attenuated inversion recovery (FLAIR) sequences were performed and correlated with diverse clinical circumstances. Three-dimensional cranial computed tomography (CT) reconstruction was obtained on one infant. Fluorodeoxyglucose positron emission tomography (FDG PET) was performed on a Siemens instrument with 3D data acquisition by lutetium oxyorthosilicate crystal. PET imaging was done on six children with GA1. Standard uptake values in μCi/cc were recorded from specific anatomic sites using Siemens region-of-interest software, and patterns of FDG uptake were compared to four age-matched disease controls.

Newborn screening for GA1 between 1988 and 1994 was based on the detection of 3-hydroxyglutaric acid (HGA) in urine, using gas chromatography-mass spectroscopy as previously described [Morton et al., 1991]. Asymptomatic newborns were targeted for testing in high-risk Amish families. Tandem mass spectroscopy-based newborn screening was established state-wide in 1994 by NeoGen, Inc. [Naylor and Chace, 1999]. Beginning in 1999, we began sequencing the GCDH gene using an ABI Prism system as described elsewhere in this supplement [see Puffenberger, 2003]. Gene sequencing is now used to confirm newborn screening results and to screen for the common Amish mutation in high-risk infants.

Identification of asymptomatic newborns prompts immediate referral to the CSC for initiation of a therapeutic care plan. Fundamental elements of "well-day" care include calories sufficient for normal growth, restriction of natural protein intake to 1–1.2 g/kg-day, supplementation with L-carnitine, and more recently a daily supplemental powder that provides lipophilic antioxidants and support for the cellular glutathione and total free sufhydryl pool (Table I). We add a source of omega-3 fatty acids to compensate for the low omega-3 fatty acid content and overabundance of omega-6 class characteristic of commercial formulas [Strauss and Morton, 2003a,b]. Protein-restricted patients are vulnerable to a variety of mineral and micronutrient deficiencies, and we routinely provide a pediatric multivitamin to make up for these potential shortfalls. Asymptomatic children younger than 2 years of age are placed on prophylactic phenobarbital, with a goal to maintain a therapeutic drug level throughout the period of peak vulnerability for acute striatal necrosis.

Parents are instructed in the preparation of a special "sick-day" diet that is high in calories (120–130 kcal/kg-day) and low in protein (0.6–0.7 g/kg-day). Ibuprofen and odansetron are used to manage fever and vomiting, respectively, at home. We maintain a low threshold for hospital admission for children under 2 years of age. Impending striatal emergencies are managed using high-calorie dextrose infusions, rapid correction of fluid deficits, high-dose intravenous carnitine and anticonvulsants (phenobarbital, fosphenytoin, and midazolam), and both specific and nonspecific measures to control inflammatory states (Table II).

TABLE I. Well-Day Diet and Medication Plan for the Infant or Young Child With GA1

Nutritional components of the "well-day" diet
Calories: 100–115 kcal/kg-day
Natural protein: 1–1.25 g/kg-day
Supplemental powder[a]: 350 mg/kg-day (max dose 8 g/day)
L-Carnitine, Creatine, and Glutamine: 100 mg/kg-day each
Riboflavin and alpha-Lipoic acid: 10 mg/kg-day each
Coenzyme Q10: 8.4 mg/kg-day
Pantothenic acid: 5.6 mg/kg-day
Alpha-linolenic acid (18:3n-3)[b]: 150 mg/kg-day
Complete pediatric vitamin[c]: 1/2 tablet daily for infants, 1 tablet for young children
Home well-day and sick-day medications
Phenobarbital: 4–6 mg/kg-day titrated to therapeutic drug level; extra dose on sick days
Ibuprofen: 10–15 mg/kg-dose q6 hours as needed for fever and inflammation
Montelukast: 5–10 mg/day as needed for signs of inflammatory disease
Ondansetron tablets: 0.15 mg/kg-dose q8 hours as needed for vomiting

[a]The supplemental powder is prepared at our clinic. Each gram of GA1 powder contains: glutamine 300 mg, creatine monohydrate 300 mg, L-carnitine 300 mg, riboflavin 30 mg, alpha-lipoic acid 30 mg, coenzyme Q10 24 mg, and calcium pantothenate 16 mg. The mixture is stored in the freezer.

[b]Alpha-linolenic (aLNA) acid is the essential precursor for long-chain polyunsaturated fatty acids docosahexaenoic and eicosapentaenoic. Flaxseed oil is 50% aLNA by weight, palatable, and well-tolerated by all of our patients. It is refrigerated and stored in a dark bottle.

[c]Flintstones and Bugs Bunny "complete" have much richer fortification than commonly used liquid vitamin preparations. These chewable vitamins can be pulverized, mixed into infant formula, and will pass through most nipples.

RESULTS

Molecular Genetics

The GCDH founder mutation among the Lancaster Amish is a C-to-T change at nucleotide 1296 within exon 11 that causes an A-to-V change at amino acid

TABLE II. Inpatient Protocol for the Prevention and Management of GA1 Acute Encephalopathic Crisis

Assessment and stabilization
Rapidly assess cardiopulmonary status, hydration, and blood glucose level
Establish IV access, ensure optimal oxygenation and cardiac output
Correct acute hypoglycemia, volume deficit, or electrolyte derangement
Reversal of catabolism
Stop all protein intake
Identify and treat infection and its associated inflammatory cascade
Antimicrobials as indicated
Antipyretics/anti-inflammatories as indicated
Dextrose therapy:
Bolus dextrose 0.5 gram/kg IV (D25%, 2 ml/kg; or as D5%NS, 10 ml/kg)
Start continuous glucose infusion of 8–10 mg/kg-min (use D10–12.5%)
Monitor bedside blood glucose q6-12 hr as needed
For hyperglycemia/glycosuria: give bolus insulin (0.1–0.2 U/kg-dose) on a sliding scale. Do not reduce the rate of dextrose infusion
Ensure the brisk output of alkaline urine
1.25–1.5X fluid maintenance; provide 4 meq/kg-day sodium
Urine output >4 ml/kg-hr
Lasix 0.5–1 mg/kg-dose as needed to avoid hypervolemia and ensure urine output
Provide 2–3 meq/kg-day bicarbonate (e.g., $NaHCO_3$) in the IV fluid if necessary to avoid systemic alkalosis but maintain urine pH 7-8
Treat vomiting with odansetron 0.15 mg/kg-dose q6-8 hr
Sedation and neuroprotection
Load L-carnitine 100 mg/kg IV over 30 min, then 100 mg/kg-dose IV q6 hr
Load phenobarbital 15–20 mg/kg IV, then 2–3 mg/kg-dose q12 hr
Load fosphenytoin 15 mg phenytoin equiv/kg IV, then 3 mg/kg-dose q12 hr, monitor levels
Consider N-acetylcysteine (NAC) IV therapy:
Dilute 20% NAC solution 1:4 in a dextrose fluid, to prepare 3% NAC
Load 140 mg NAC/kg IV over one hour using 0.2 micron filter
Give 70 mg/kg-dose IV over one hour q4 hr, for minimum of 48 hr
Monitor for symptoms and signs of anaphylaxis
Consider: Measures to reduce CSF production and ICP;
If hydrocephalus appears to be distorting, stretching, or compressing middle fossa bridging veins:
Lasix 0.5–1 mg/kg-dose IV q6-8 hr
Acetazolamide 7–10 mg/kg-dose IV q8 hr

421. The mutation is postulated to impair tetramer assembly [Goodman et al., 1998]. Enzyme activity in fibroblasts of affected Amish patients is 0–12% of control values [Morton et al., 1991]. The majority of affected Amish infants are homozygous for c.1262C->T, and a significant number of affected non-Amish patients are heterozygous for this base change.

In non-Amish infants an array of mutations affect 9 of the 11 exons in the GCDH gene. Compound heterozygosity is common. From 15 non-Amish haplotypes, c.1262C->T is found in 9 of 30 mutant GCDH genes, consistent with the early European origin of this mutation [Goodman et al., 1998; Busquets et al., 2000; Zschocke et al., 2000]. There is no obvious correlation between specific mutations and disease severity, and protein changes that allow residual enzyme activity do not appear to confer protection against striatal injury. Variable severity occurs within sibships homozygous for the Amish mutation, suggesting a critical role for other genetic and environmental variables in disease expression.

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Biochemistry

Analysis of methoximated urine organic acids by gas chromatography-mass spectroscopy [Morton et al., 1991] in affected Amish neonates typically shows massive elevations of glutarate (GA), moderately high adipate, and small but significant elevations of both glutaconate (GC) and 3-hydroxyglutarate (HGA) (Table III). Lactic aciduria and generalized tricarboxylic or dicarboxylic aciduria are absent, except in children under significant physiologic stress. 3-Hydroxyglutarate is disease specific and is the only diagnostic metabolite in some samples, but is occasionally detected in trace amounts in urine from healthy subjects. Selective ion monitoring is required to detect pathological HGA concentrations as low as 0.2 μmol/mmol Cr in a few patients. Plasma levels of GA range from 0 to 6 μmol/l, compared to lower HGA levels of 0.01–0.1 μmol/l. Cerebrospinal fluid (CSF) metabolite concentrations are scarcely detectable, but are in general <10% of plasma levels. The putative cellular origin of circulating organic acids is shown in Figure 1.

Affected patients have average daily excretion rates of GA and HGA of 2000 and 20 μmol/kg-day, respectively. These values do not capture the extreme inter- and intraindividual diversity of organic acid production in our patients (Table III and Figure 2). Glutaric acid measurements in particular are highly variable over time, compared to HGA values, which are lower but more consistent.

TABLE III. Select Laboratory Values in Patients With GA1

	Patients	Controls
Urine (μmol/mmol Cr)		
Glutarate (GA)	3–3500	0–45
3-hydroxyglutarate (HGA)	0.2–305	Trace
HGA/GA ratio	0.07–5.14	N/A
Blood (μmol/l)		
Glutarate	0–6	<1
3-hyrodoxyglutarate	0.01–0.1	Undetectable
HGA/GA ratio	0.01–1.72	N/A
Newborn		
Glutarylcarnitine	0.3–0.7	Undetectable
Total carnitine	18	15–300
Total acylcarnitine	11	5–60
Carnitine-supplemented infants		
Glutarylcarnitine	0.5–0.9	Undetectable
Total carnitine	40–60	25–125
Total acylcarnitine	10–20	5–20
Daily excretion rate (μmol/kg-day)		
Glutarate	0.3–4000	N/A
3-hydroxyglutarate	0.1–33	N/A

Cr, creatinine; N/A, not applicable.

Three temporal patterns are evident in our patients. The majority of Amish infants excrete large amounts of GA at birth, which decline to normal levels over the first year of life in parallel with a quantitatively smaller decrease of HGA. Other patients continue to be high excretors of GA into childhood. Finally, several non-Amish patients are born with normal GA acid excretion, detectable concentrations of HGA, and an HGA:GA ratio in plasma and urine that always exceeds 1. Striatal injury can be associated with any of these excretion patterns and does not routinely coincide with organic acid elevations (Fig. 2).

Pathological metabolites can be detected in blood and urine as conjugates of carnitine or glycine. The intramitochondrial generation of glutarylcarnitine, and its subsequent excretion through urine and bile, depletes carnitine from the body. This process begins in utero, evidenced by consistently low total carnitine levels in all newborn infants with GA1 that we have tested. Glutarylcarnitine is the circulating metabolite detected by tandem mass spectroscopy-based newborn screening [Naylor and Chace, 1999]. Concentrations in dried filter specimens of our patients are typically 0.3–0.7 μmol/l at birth, and 50–60% of total carnitine is esterified. Glutarylcarnitine only accounts for a small percentage of the esterified fraction, which is predominantly acetylcarnitine. Oral carnitine supplementation increases whole-blood free carnitine by three- to fourfold, but does not significantly affect blood concentrations of glutarylcarnitine or esterified carnitine.

Clinical Manifestations

Early diagnosis and prospective care reduces neurological disability

Clinical characteristics of 37 Amish and 40 non-Amish patients are summarized in Tables IV and V. The Amish group is divided into those identified retrospectively (n = 17) and those treated prospectively following diagnosis through screening of asymptomatic newborns (n = 20). In all groups, basal ganglia degeneration is the major determinant of functional disability. The incidence of basal ganglia injury is 85% in non-Amish patients and 94% in retrospectively identified Amish children. Over half of Amish patients were diagnosed by neonatal screening. The basal ganglia injury rate is 35% in the 20 Amish children managed prospectively following early diagnosis. The majority of non-Amish patients were diagnosed between 1988 and 2000 after presenting with neurological disability. Only two of these non-Amish children were diagnosed as asymptomatic newborns, and they remain healthy.

Micrencephalic macrocephaly is a distinctive radiologic feature of GA1

In the majority of neonates, an enlarged head circumference is the only presenting sign of GA1 (Fig. 3).

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MR or CT imaging at birth typically shows an underdeveloped neocortex and diffuse expansion of the CSF space. The rostrolateral frontal, opercular, and anterior temporal lobes may be particularly hypoplastic, but with a well-developed gyral pattern. Hypoplasia of the frontal lobes may be accompanied by an underdeveloped intermediate fiber zone and thin corpus callosum. The combination of fronto-operculo-temporal hypoplasia and communicating hydrocephalus creates a distinctive radiologic appearance that may be patho- gnomonic for GA1.

Fluid collections in the middle cranial fossae are large. Veins can be seen stretching tenuously across this space and are subject to distortion and rupture (Fig. 4). Thirteen percent of non-Amish patients developed acute subdural hemorrhage after minor head trauma, and in two cases, this was accompanied by retinal hemorrhages.

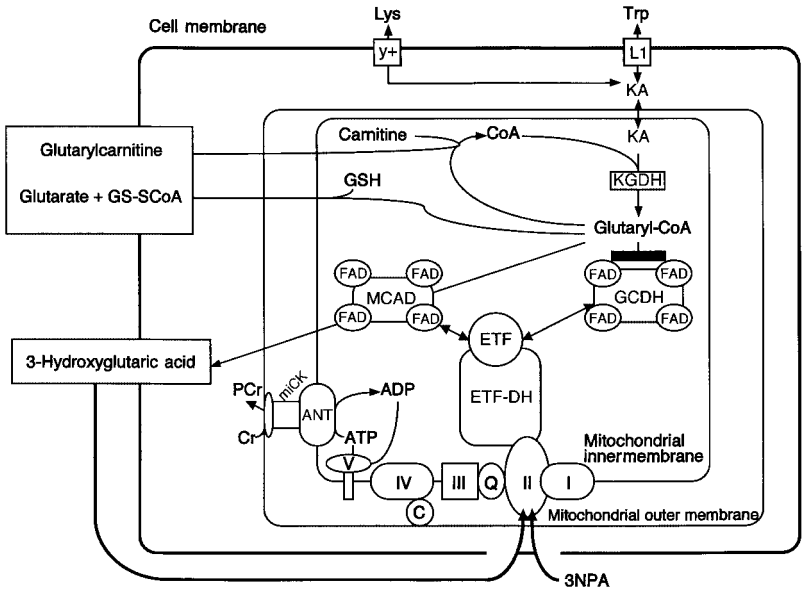

Figure 1. Cellular metabolism of lysine and tryptophan in GA1. Lysine and tryptophan enter cells through distinct sodium-independent facilitative amino acid transporters. Lysine competes with arginine, ornithine, and homoarginine for uptake via the y+ system. Tryptophan is carried into cells by L1, competing with branched-chain amino acids, phenylalanine, tyrosine, methionine, threonine, and histidine. These amino acids are converted to ketoadipic acid (KA) in cytosol through glutamate/ketoglutarate-coupled transamination. Ketoadipic acid is transported into mitochondria, and its oxidative decarboxylation is assumed to be mediated by alpha-ketoglutarate dehydrogenase. This reaction utilizes free CoA to form glutaryl-CoA, which cannot be metabolized further by the mutant GCDH enzyme. Glutaryl-CoA can undergo conjugation with carnitine to form glutarylcarnitine and free CoA or can be further oxidized by medium-chain acyl-CoA dehydrogenase (MCAD) to form 3-hydroxyglutaryl-CoA. A putative though unproven interaction with reduced mitochondrial glutathione (GSH) would form a glutathione-CoA oxidized disulfide and free glutaric acid. Noncovalently bound flavin groups of both GCDH and MCAD normally interact with electron transfer flavoprotein (ETF) and its dehydrogenase to shuttle electrons to complex II (succinate dehydrogenase) of the electron transport chain. Both HGA and 3-nitropropionic acid (NPA) can inhibit this complex in vitro, though the latter is much more potent.

Investigation of child abuse preceded a metabolic diagnosis in three of these children. Beyond the vascular risk during infancy, the functional significance of neocortical hypoplasia is unknown. In the absence of a superimposed basal ganglia injury, our patients with significant frontotemporal hypoplasia do not have clinically apparent psychomotor dysfunction, though they have not been subjected to formal cognitive testing.

Abnormal white matter signal is a rare radiologic finding in Amish children

Of patients who underwent cranial imaging, 1/17 Amish (6%) and 10/31 non-Amish (32%) patients have variable T2, DWI, and FLAIR signal hyperintensity in the frontal and parietal intermediate fiber zones. Unlike the intermediate zone hypoplasia that can accompany micrencephalic macrocephaly, the volume of subcortical white matter tracts may be normal in these patients (Fig. 5). Signal quality of intracortical U fibers is characteristically preserved. Early myelinating tracts of the dorsal brain stem, cerebellar peduncles, posterior internal capsules, optic tracts, and radiations appear normal. Like frontotemporal hypoplasia, these radiologic findings are not understood mechanistically and are of unclear clinical significance in GA1. They certainly do not have the ominous implication they do in other leukodystrophies (i.e., metachromatic leukodystrophy), and thus different biological mechanisms may be involved. Older GA1 patients with significant T2 and FLAIR hypersignal and intact basal ganglia could have normal motor function and neurocognitive performance.

Acute striatal necrosis is the major cause of morbidity and mortality

Clinically abrupt stroke-like putaminal necrosis is the most distinctive and crippling manifestation of GA1, and the major determinant of both morbidity and mortality. Most patients (78%) are diagnosed *after* they develop striatal necrosis, and their outcomes are poor. Basal ganglia injury can extend through various deep nuclei, but the lesion is always histologically continuous and the putamen is consistently involved. In nearly all patients for whom information is available, neurological deterioration was abrupt. Parents typically recall the date and time it occurred. In both

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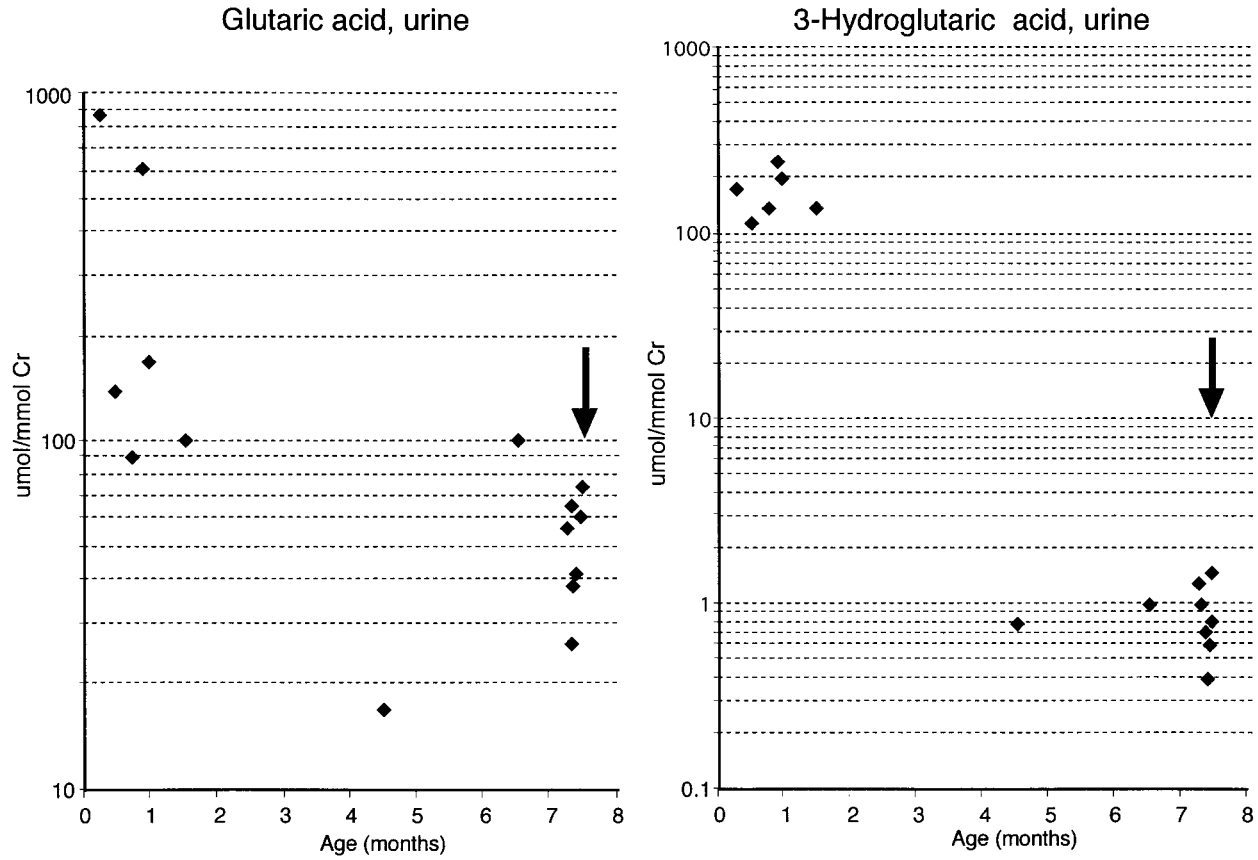

Figure 2. Urine organic acids in infants affected with GA1 typically show very high glutaric acid (GA) and detectable HGA at birth. Both levels may drop considerably over the first year of life, with GA actually decreasing into the normal range. The HGA concentration remains elevated in plasma and urine of all our brain-injured patients, although the concentration is still relatively low. Acute striatal necrosis (arrow) occurred in this non-Amish boy at age 7.5 months following a remarkable decrease in GA and HGA excretion that occurred between 2 and 6 months of age (note log 10 scale of ordinate). Clinically profound and MRI-confirmed acute brain injury developed during a 7-day intercurrent illness during which GA and HGA plasma concentrations did increase, but still peaked at relatively low values of 6 and 0.06 μmol/l, respectively.

patient groups, onset of injury is between 2 and 18 months, with a peak window of susceptibility from 6 to 14 months. No child in our cohort developed basal ganglia injury after the second birthday.

Acute neurological crisis is typically precipitated by a common childhood infection accompanied by fever, a nonspecific acute phase response, and some degree of dehydration. Children experience behavioral arrest with the onset of either profound hypotonia or diffuse rigidity. This may be accompanied by depressed consciousness, seizures, or dystonic extremity movements. Neurological deterioration is uniformly associated with tissue swelling and necrosis of basal ganglia gray matter (Fig. 6). Signal abnormalities characteristically begin in the posterior, dorsal, and lateral aspects of the putamen and evolve continuously in a forward and medial direction to involve the caudate heads and pallidi to a variable degree. Over ensuing weeks, infarcted tissue is replaced by a thin gliotic strip. The severity of residual dystonia appears directly related to the volume of tissue destroyed (Fig. 7). The nature of precipitating illness, systemic acidosis, and organic acid patterns either preceding or at the time of neurological injury do not allow us to predict the onset or extent of striatal necrosis in individual patients, nor does treatment of systemic biochemical derangements insure good neurological outcome. However, infectious illness, dehydration, and *delays* in treatment are clearly risk factors for severe injury.

Irreversible tissue destruction has already occurred in most children presenting with acute flaccidity, rigidity, or dystonic posturing. Of 57 patients diagnosed because of clinical signs, 74% are fully disabled by dystonia. Fourteen percent have mild to moderate dystonia with an abnormal gait and uncontrolled movements, but are able to sit, walk, eat, and dress independently. Only 12% have no apparent motor impairment. Injuries acquired at an early age tend to be more severe, and we observe a higher injury rate in males, regardless of whether they are prospectively or retrospectively diagnosed (Fig. 8). Cultural-genetic background in our cohort (i.e.,

TABLE IV. Neurologic and MRI Findings in Amish GA1 Patients (n = 37)

	Clinical features				Neuroradiologic features[a]						
Patient no.	Current age (yrs)	Age at diagnosis	Crisis onset age (mos)	OFC (centile)	Dystonia	Dyskinesia	Dysarthria/ dysphagia	Hydrocephalus	Putamen lesion	Caudate lesion	Pallidum lesion
Patients diagnosed after the onset of neurologic symptoms 1988–1990											
A1	D12	5 yrs	14	90	++	Athetosis	++	+			
A2[b]	42	28 yrs	2	40	+	Chorea	+				
A3	27	15 yrs	11	60	++	Athetosis	++	++	++	++	
A4	24	12 yrs		>95	−	−	−	++	+		+
A5[b]	17	5 yrs	6	50	++	Athetosis	++				
A6[b]	D19	16 yrs	15		++	Athetosis	++				
A7[b]	D7	7 yrs	6		++	Athetosis	++				
A8	21	9 yrs	3	95	++	Athetosis	+	+	++		
A9[b]	D2.5	2.5 yrs	5	30	++	Athetosis	++				
A10[b]	D6.5	6.5 yrs	6	25	++	Athetosis	++				
A11	23	11 yrs	2	95	+	Chorea	+	+	++		
A12[b]	15	3 yrs	18	60	++	Chorea	++				
A13[b]	12	0.6 yrs	6	95	++	Athetosis	++				
A14	10	0.5 yrs	3	25	++	Athetosis	++		++		
A15[b]	11	1 yrs	15	>95	++	Athetosis	++				
A16[b]	10	0.5 yrs	27	50	++	Athetosis	++				
A17	5	10 yrs	10	>95	++	Athetosis	++	++	++	++	+
Presymptomatically diagnosed patients treated with specific prophylactic care 1989–2002											
A18	11	5 mos		>95	−	−	−				
A19	9	1 day		>95	−	−	−				
A20	10	3 days	2	>95	++	Athetosis	++	+	++	++	
A21	9	1 day	8	75	+	Chorea	++				
A22	6	1 day		>95	−	−	−				
A23	6	10 days	7	48	++	Athetosis	++	+	++	+	+
A24	5	3 mos		>95	−	−	−				
A25	5	1 day		>95	−	−	−	+			
A26	5	7 days		>95	−	−	−				
A27	3	7 days		>95	−	−	−	+			+
A28	D	8 days		20	−	−	−				
A29	3	7 days		>95	−	−	−	+			
A30	3	8 days		>95	−	−	−				
A31	1	7 days	8	90	+	Athetosis	+	++	++		++
A32	0.5	10 days		50	−	−	−				
A33	1	7 days	6	50	+	Chorea	−				

A34	1.5	7 days	12	>95	++	Athetosis	++	++	++	++	++
A35	1	6 days		75	−	−	−	++			
A36	1	6 days	6	>95	+	Chorea	−	++			
A37	0.5	7 days	Neonate	>95	−	Chorea	−	++	+	+	+

[a]In contrast to non-Amish patients, no Amish patients suffered subdural bleed or injury to the substantia nigra.
[b]MRI films not available for review.
−, normal; +, mild to moderate; ++, severe.

TABLE V. Clinical and Neuroradiologic Features of Non-Amish GA1 Patients (n = 40)

	Clinical features						Neuroradiologic features						
Patient no.	Current age (yrs)	Crisis onset age (mos)	OFC (centile)	Dystonia	Dyskinesia	Dysarthria/ dysphagia	Hydrocephalus	Putamen lesion	Caudate lesion	Pallidum lesion	Substantia nigra lesion	Leukodystrophy	Subdural bleed
N1	7		>95	+	Chorea	+	+			+	+	+	
N2	D9[a]	8	75	++	Athetosis	++		++	++	+			
N3	4		>95	++	Athetosis	++	++	++	++	++		++	
N4	21		>95	++	Athetosis	++	++	++					
N5	D10			++	Athetosis	++	++	++					
N6	4	12	>95	++	Chorea	++	++	++		++	++		
N7	10		>95	−	−	−	+			+		++	
N8	15		>95	++	Athetosis	++	N/A						
N9			>95	++	Athetosis	++	N/A						
N10			>95	−	−	−	N/A						
N11	3		>95	++	Athetosis	++	++	++		++	+	++	
N12	10		>95	++	Athetosis	++	++	++	++				
N13	2		>95	++	Athetosis	++	N/A						
N14	10	12	>95	++	Athetosis	++	++	++	++				+
N15	6		>95	++	Athetosis	++		++	++	+			
N16	3		>95	−	Athetosis	−	++					++	
N17	19	6	>95	++	Athetosis	++	++	++				++	
N18	7		>95	++	Athetosis	++	++	++	++	+			
N19	22			++	Athetosis	++	N/A						
N20	19			++	Athetosis	++	N/A						
N21	19			−	−	−	N/A						
N22	7	11	50	++	Athetosis	−	+	++		+		+	

(*Continued*)

TABLE V. (*Continued*)

	Clinical features						Neuroradiologic features						
Patient no.	Current age (yrs)	Crisis onset age (mos)	OFC (centile)	Dystonia	Dyskinesia	Dysarthria/ dysphagia	Hydrocephalus	Putamen lesion	Caudate lesion	Pallidum lesion	Substantia nigra lesion	Leukodystrophy	Subdural bleed
N23	11	6	75	++	Rigid	+	++	++	++	++	+	+	
N24	13		>95	–	–	–	+						+
N25	7	6	>95	++	Chorea	+	N/A				++	++	
N26	5		>95	++	Athetosis	++	+	++	+	++			
N27	3			+	Chorea	+	++	+		+			
N28	8		>95	++	Athetosis	+	++	++	++	++			
N29	3			+	Chorea	+	+	+		+			
N30	6	11	>95	++	Athetosis	++	+	++	++	++			
N31	3			++	Athetosis	+	N/A						
N32	2	11		++	Athetosis	–	+	+	+	+	++		+
N33	6			–	–	–	+	+					
N34	3			+	Chorea	–		+					
N35	2	5	>95	++	Athetosis	++	++	++	++				
N36	12		>95	+	Chorea	–	+	+				++	
N37	1		>95	++	Chorea	+	+	++		+			
N38	5	6	>95	++	Athetosis	++	++	++		++		++	
N39			>95	++	Athetosis	++	N/A						
N40	3	11	>95	+	Chorea	++	++	+				++	+

[a]D9 means died at 9 years.
–, normal; +, mild to moderate; ++, severe.
N/A, MRI not available.

Amish vs. non-Amish) does not significantly influence neurological outcome, while detection of asymptzomatic newborns decisively reduces the risk of brain injury (Fig. 8).

FDG PET and intraoperative electrical recording give us insight into the effect of putaminal destruction on brain physiology (Fig. 7). Complete loss of both direct and indirect striatopallidal projections essentially disconnects the deeper basal ganglia structures from ongoing thalamocortical activity and isolates them from afferent modulation. The normally strong excitatory pulse frequency of the subthalamic nucleus is substantially reduced, reflected in diminished and chaotic firing of the internal pallidum. Sustained nonreciprocal activations of the lower motor neuron pool result from a loss of inhibitory basal ganglia modulation on both the thalamocortical system and the descending pedunculopontine-reticulospinal tract [Brodal, 1981; Nakano et al., 1995; Shima et al., 1995; Obeso et al., 1997; Berry et al., 1999].

Dystonia causes chronic medical and surgical complications

Dystonia is a neurological phenomenon with several cardinal features. Agonist and antagonist muscle groups co-contract, leading to dynamic torsional deformities, a failure of reciprocal inhibition, and postural instability. Relaxation and sleep characteristically alleviate dystonia, while fear, excitement, and pain make it worse. Despite profound motor impairment, intelligence is relatively preserved if injury is confined to the putamen. Patients with caudate degeneration appear to have significant cognitive dysfunction.

Dystonia interferes with talking, swallowing, airway reflexes, breathing, and voluntary movements. Abnormal muscular forces deform the developing skeleton and can dislocate joints. Nonspecific medical and surgical complications caused by dystonia are the primary reason for office visits, hospitalizations, and surgeries in affected patients (Table VI). Respiratory problems are the major cause of early mortality.

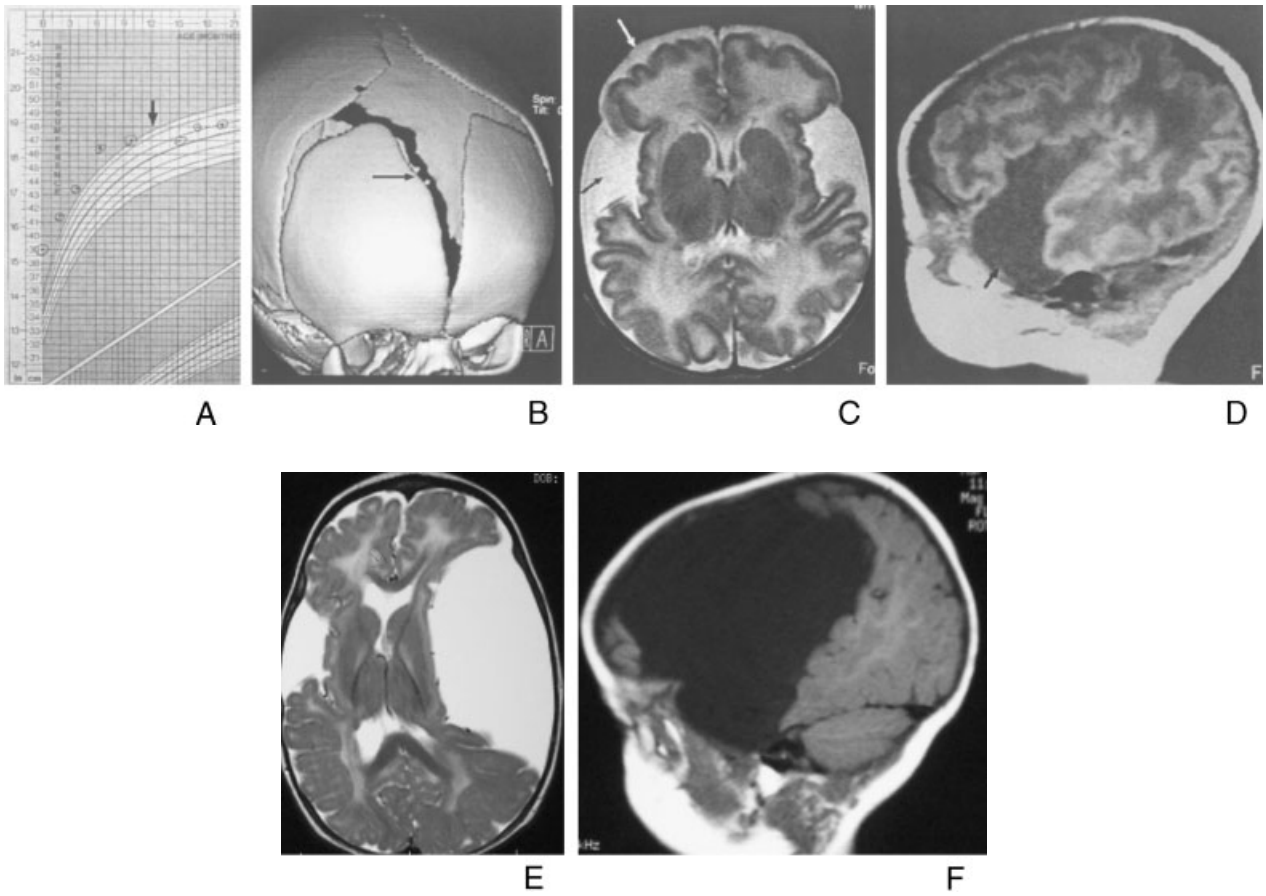

Figure 3. Micrencephalic macrocephaly. Seventy percent of our patients are born with an occipitofrontal head circumference of >95th percentile, and fontanelles are often bulging in asymptomatic neonates. **A:** Head growth generally increases on a stable trajectory and then may decelerate between 6 and 8 months of age, preceding development of acute striatal necrosis (arrow). **B:** Cranial CT scan with 3D reconstruction shows widely split cranial sutures (arrow) and fontanelles (arrowhead) of communicating hydrocephalus in a neonate. CSF from these infants may have a mildly elevated opening pressure, increased protein level, and high pH. Red blood cells and xanthochromia may also be present. **C** (axial): Cranial MRI of an asymptomatic newborn shows mild enlargement of the cerebral ventricles and expansion of the fluid spaces around the brain stem and over the cerebral convexities. Fluid collections are most evident over the frontal lobe (white arrow) and in the middle cranial fossae (black arrows); the underlying frontal, anterior temporal, and opercular cortices are hypoplastic. In contrast, the basal ganglia appear normal. **D:** With advancing age, the fluid space around the brain may increase, in part a reflection of poor brain growth and a hypoplastic intermediate fiber zone. **E** (coronal) and **F** (sagittal): In three patients, true arachnoid cysts developed in the middle cranial fossae and were devoid of radiologically evident bridging veins. This massive left-sided cyst was present at age 10 months in the patient depicted as a neonate in panel C. It was found incidentally, it was not surgically decompressed, and he remained completely asymptomatic. Note T2 hypersignal of terminal zone white matter and the internal pallidi.

Dystonia in GA1 is difficult to treat. Medications that normally act on striatal receptors are generally ineffective. Severely disabled children benefit from nonspecific centrally acting muscle relaxants, such as lioresal and diazepam, but these drugs do not restore function. In patients with residual motor function, some improvement in choreoathetosis can be achieved with anticholinergic agents such as trihexyphenyl. Ourexperience with a 4-year-old non-Amish boy and an 11-year-old Amish boy suggests that in contrast with idiopathic torsion dystonia, stereotactic pallidotomy does not restore function in children with GA1, though it may reduce the force of dystonic contractions.

Exercise intolerance, hypoglycemia, and seizures can develop in older patients

Children who escape basal ganglia injury have been generally healthy on follow-up, but nonetheless have some chronic problems attributable to GA1. Fatigue and exercise intolerance are common. Fasting hypoglycemia can occur in children at any age, and probably has two distinct causes in GA1. Nonketotic hypoglycemia results from carnitine deficiency, which can also give rise to myopathy, cardiomyopathy, and Reye-like hepatocerebral crisis. Even in carnitine supplemented children, hypoketotic hypoglycemia can occur during intercurrent illness. In brain-injured patients, violent dystonic movements and postures are frequently *misdiagnosed* as seizures, but true electrophysiologic seizures can develop in older children with or without striatal degeneration.

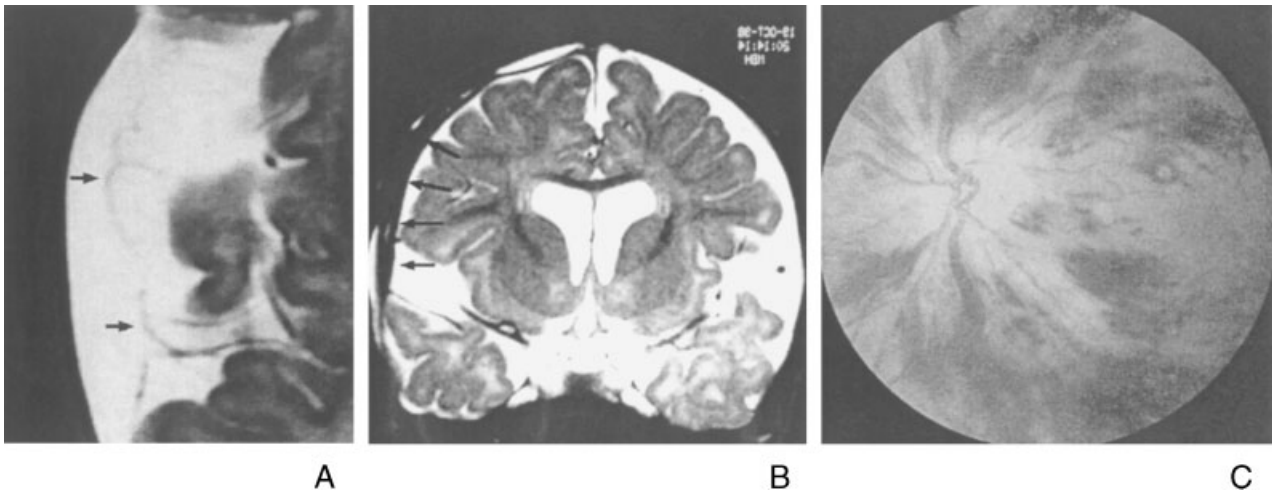

Figure 4. Bridging veins, subdural hematoma, and acute retinal hemorrhages. **A:** Medium-caliber veins can be seen stretching across the middle cranial fluid spaces in an asymptomatic infant with GA1 (arrows). These vessels are subject to compression, distortion, and rupture. **B:** Coronal T2 MRI shows massive subdural hemorrhages (arrows) in an infant who became encephalopathic after falling a short distance from a rocking horse. **C:** The sudden increase in intracranial veinous pressure associated with acute subdural bleeding can cause retinal hemorrhages in children with GA1.

These are usually brief, generalized, and easily controlled with anticonvulsant monotherapy.

DISCUSSION

Targeted screening for GA1 began at CSC in 1988, and general population screening in Pennsylvania was introduced in 1994 [Naylor and Chace, 1999]. This combined effort has identified 20 asymptomatic Amish neonates over 11 years. Sixty-five percent of these children remain healthy (Fig. 8C). Thus, knowledge of the underlying condition, disease-specific prophylactic care, and aggressive management of common childhood illnesses improves outcome, and in particular reduces the incidence of striatal necrosis. Despite significant progress in the care of GA1, current therapy remains inadequate and morbidity is high among patients with dystonia. In our series, all physically impaired children have been resistant to pharmacotherapy. While agents such as diazepam and lioresal can produce muscle relaxation, they do not restore function, and at doses sufficient to relax skeletal muscle, these drugs cause significant sedation.

GA1, like other genetic-metabolic diseases, is difficult to study by currently accepted standards of medical evidence. For diseases that are rare in the general population, small patient numbers limit the statistical power afforded by large placebo-controlled trials, and substantial regional differences in screening and patient care are a barrier to general consensus. With controlled clinical data sets lacking, many genetic-metabolic practitioners turn to the ever-expanding molecular biology literature to provide guidance for optimal care. However, precise knowledge of gene mutations and enzyme function does not instruct us about how to care for patients. One of the important messages of the last decade is that the study of gene mutations has only a limited role in elucidating the complex biological interactions that occur in whole organisms [Dauphinee and Martin, 2000].

While clinicians and families await the development of strategies to repair genes, children continue to suffer with GA1, and the pathophysiology of acute striatal necrosis remains largely unknown. Without early diagnosis, 80–90% of affected infants will come to an emergency room between 6 and 18 months of age with an evolving brain injury that will lead to lifetime disability. Diagnosis during acute neurological crisis is delayed by multiple factors, including workups for more common pediatric conditions, misconceptions about the acute presentation of metabolic disease, controversies over newborn screening, investigations of child abuse, and delays associated with in-hospital consultations and processing of laboratory tests [Dunger and Snodgrass, 1984; Iafolla and Kahler, 1989; Sugiyama et al., 1990; Osaka et al., 1993; Woelfle et al., 1996; Renner et al., 1997; Thomason et al., 1998; Nyhan et al., 1999; Busquets et al., 2000; Kafil-Hussain et al., 2000; Hymel et al., 2002].

Striatal injury in GA1 is a *stroke* in the formal sense: "something likened to a blow in its effect, as in causing pain, injury, or death; an attack of apoplexy or paralysis" [Stein, 1980]. Like cerebrovascular occlusion in adults, elucidation of such a process is of profound clinical importance. Based on our own observations, reports of other clinicians, and a careful reading of the literature, we have forwarded a series of concepts that may illuminate brain injury in GA1 and allow us to use targeted therapies

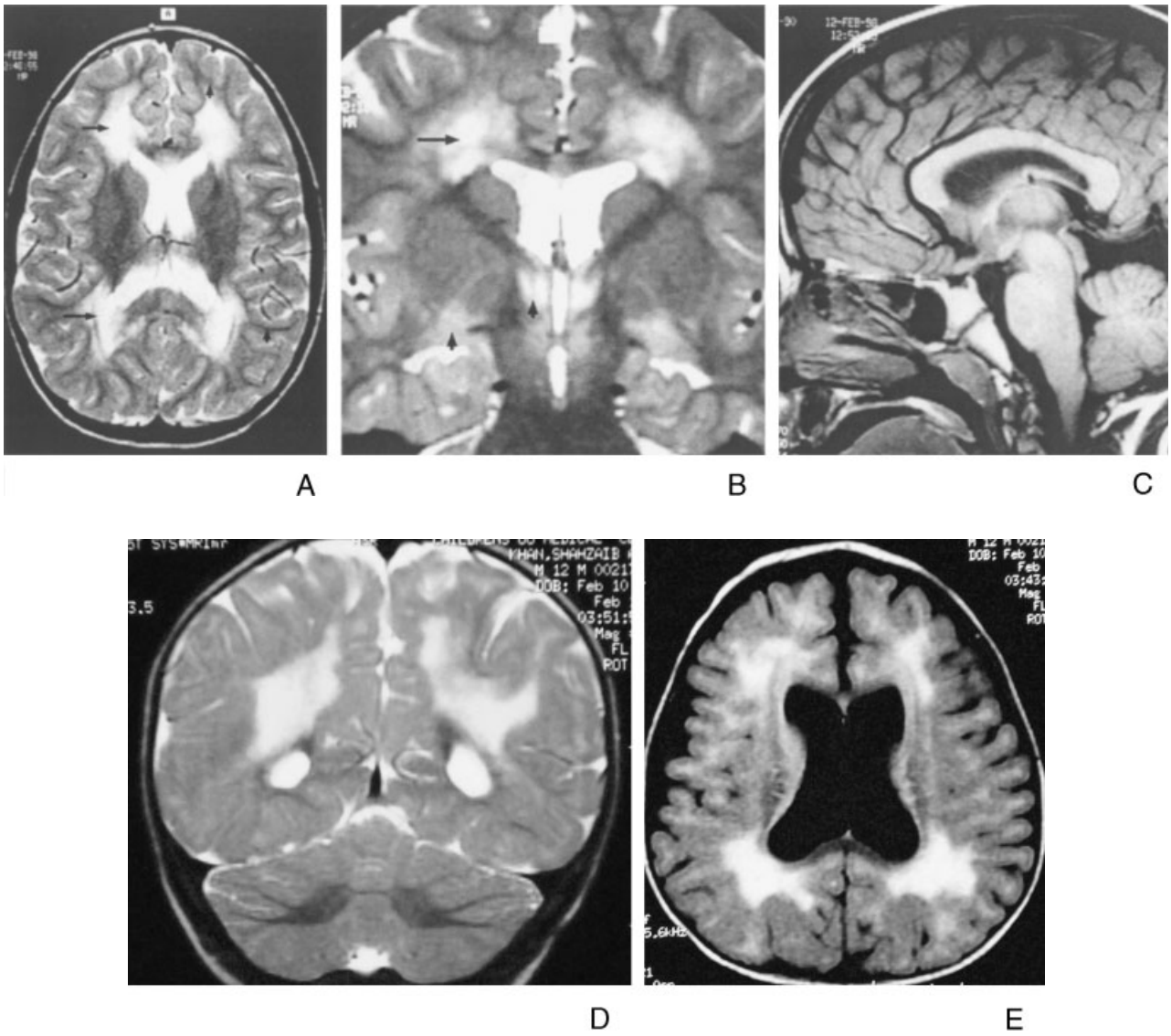

Figure 5. White matter abnormalites in GA1. **A:** axial, **B:** coronal, and **C:** sagittal. Twenty-five percent of non-Amish GA1 infants have an abnormal T2 hyperintense signal of supratentorial white matter that persists into childhood. Early myelinating structures appear normal, as does the volume of subcortical and interhemispheric fiber tracts. The T2 signal is particularly high in the periventricular regions of the frontal and parieto-occipital lobes (arrows) and preserved in the arcuate U fibers (arrowheads). B: On coronal view, patchy demyelination is evident in the perventricular white matter and genu of the corpus callosum. T2 hyperintensity is also seen in the gray matter of the basal and medial septal nuclei (arrowheads). C: On sagittal view, the volume and signal of the corpus callosum are normal. **D** (coronal): Terminal zone hypersignal contrasts with the normal appearance of early-myelinating cerebellar peduncles. **E** (axial): FLAIR imaging shows the extent of subcortical white matter abnormality in a 12-month-old patient.

during crisis. Clinical and experimental foundations for these concepts are presented as a companion paper [Strauss and Morton, 2003b].

Our current model of GA1 forms a basis for a specific prophylactic regimen (Tables I and II) involving the use of protein restriction, L-carnitine, creatine monohydrate, glutamine, lipophilic antioxidants, nonspecific anti-inflammatory agents, and both prophylactic and acute intravenous anticonvulsants [Duncan, 2000; Reiter et al., 2000; Binienda et al., 2001; Brustovetsky et al., 2001; Tarnopolsky and Beal, 2001]. It is important to emphasize that our care strategy is constantly evolving on the basis of new observations and scientific discoveries. It is *one* approach to care, rather than *the only* approach, and we have tried to present it in sufficient detail to allow comparison with the

It is important to emphasize that our care strategy is constantly evolving on the basis of new observations and scientific discoveries.

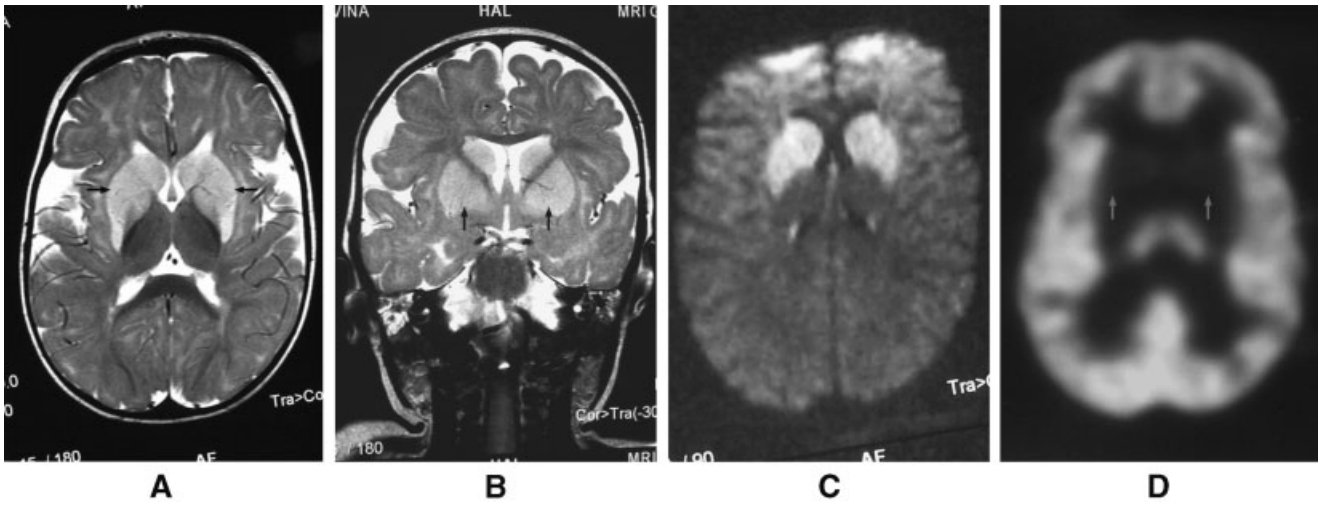

Figure 6. Acute striatal necrosis. Injury to the striatum in GA1 is typically acute and stroke-like. A 1-year-old Amish infant developed abrupt onset of behavioral arrest and lost postural control in the setting of fever, dehydration, *E. Coli* urinary tract infection, and bronchiolitis. **A** (axial) and **B** (coronal): Cranial MRI within 24 hr of the onset of the neurological syndrome shows focal symmetric tissue swelling and T2 hyperintensity that is continuous throughout the basal ganglia (arrows). **C:** The smaller diffusion-weighted signal is restricted to the infarcted area. **D:** FDG PET imaging on hospital day 6 shows striatal FDG uptake reduced to about 50% of the expected value (red arrows). Over the ensuing weeks, the patient developed severe dystonia as the putamina were replaced by slit-like gliosis. At 20 months of age, she was unable to speak, eat, sit, or use her hands.

practice of others. The present data and pathophysiologic model have two strengths: 1) the concepts forwarded are easily testable, in both tissue culture and whole animals; and 2) results of such studies could lead directly to improved therapy with agents such as N-acetyl-cysteine, intravenous phosphocreatine, more potent anti-inflammatory or anti-cytokine drugs, and compounds that specifically modulate dopaminergic transmission and vascular phenomena [Dux and Joo, 1982; Dux et al., 1990; Tuor, 1997; Pahan et al., 1998; Han et al., 1999; Abbott, 2000; Fontaine et al.,

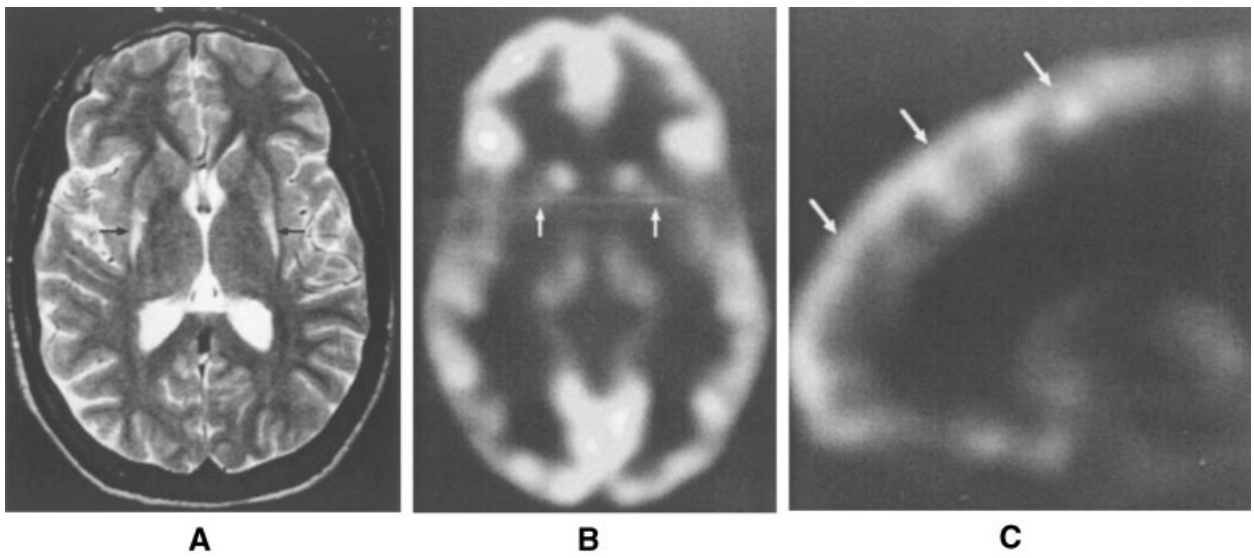

Figure 7. Neuroanatomy and physiology of dystonia. **A:** Cranial MRI in an 11-year-old Amish boy shows the chronic sequelae of striatal necrosis. In general, the degree of dystonia, and thus long-term neurological prognosis, is directly related to the volume of putamen destroyed (volume loss and gliosis, arrow). **B** and **C:** FDG PET in axial (B) and sagittal (C) views shows severe hypometabolism of the dorsal putamen, with small nubbins of functional tissue anteriorly (panel B, red arrows). Caudate metabolism is preserved. There is overactivity of the frontal neocortex (panel C, red arrows). This patient has an abnormal gait and hyperkinetic choreoathetosis, but is able to walk, dress, and eat independently.

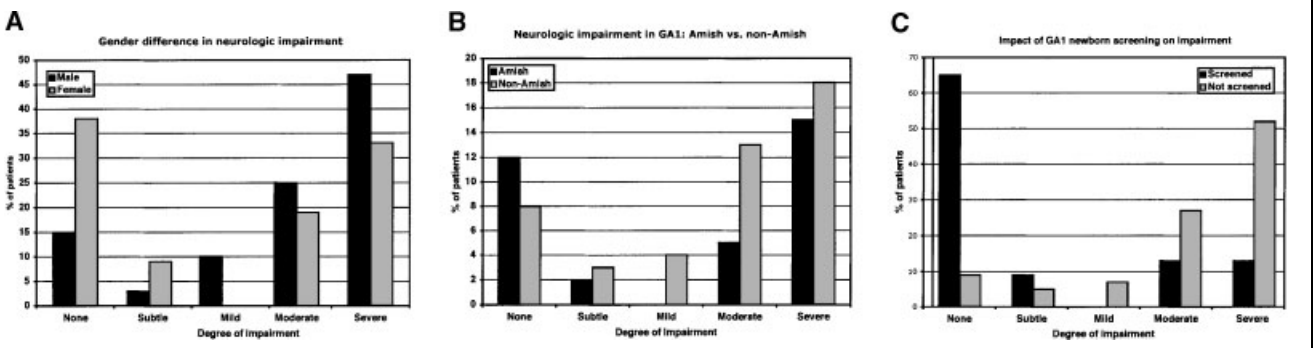

Figure 8. **A:** Males with GA1 are at slightly higher risk for basal ganglia injury and neurological impairment than females. **B:** Amish genetic background does not significantly affect outcome in our cohort. **C:** Identification of asymptomatic newborns significantly reduces the prevalence of neurological impairment. None = no evidence of injury; Subtle = mild extremity dystonia noted by exam only; Mild = chorea or dystonia, but able to perform all daily living activities independently; Moderate = significant dystonia, but able to speak and ambulate with assistance; Severe = crippling dystonia, wheelchair bound, completely dependent for all daily activities.

TABLE VI. Chronic Complications of Dystonia

Nutrition and metabolism
Intermittent hyperthermia
Impaired chewing and swallowing
Gastroesophageal reflux
Skin and dentition
Decubitus ulcers
Poor dental care, increased virulence of aspirated organisms
Skeletal
Joint dislocation and pain
Scoliosis and chest wall deformity
Long-bone deformity and fracture
Disuse osteoporosis
Pulmonary
Impaired defensive airway reflexes
Laryngeal dystonia and stridor
Acute aspiration pneumonitis
Chronic aspiration pneumonia
Chest wall dystonia embarrassing respiratory mechanics
Development
Impaired speech, writing, and expressive language
Inadequate access to educational services
Absolute dependence on others for daily living

2000; Muruganandam et al., 2000; Patnaik et al., 2000; Schulz et al., 2000; Gilgun-Sherki et al., 2001; Shibata et al., 2001].

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