Glutaric acidemia type 1: Treatment and outcome of 168 patients over three decades

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Glutaric acidemia type 1: Treatment and outcome of 168 patients over three decades


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ABSTRACT

Glutaric acidemia type 1 (GA1) is a disorder of cerebral organic acid metabolism resulting from biallelic mutations of GCDH. Without treatment, GA1 causes striatal degeneration in > 80% of affected children before two years of age. We analyzed clinical, biochemical, and developmental outcomes for 168 genotypically diverse GA1 patients managed at a single center over 31 years, here separated into three treatment cohorts: children in Cohort I (n = 60; DOB 2006–2019) were identified by newborn screening (NBS) and treated prospectively using a standardized protocol that included a lysine-free, arginine-enriched metabolic formula, enteral L-carnitine (100 mg/kg•day), and emergency intravenous (IV) infusions of dextrose, saline, and L-carnitine during illnesses; children in Cohort II (n = 57; DOB 1989–2018) were identified by NBS and treated with natural protein restriction (1.0–1.3 g/kg•day) and emergency IV infusions; children in Cohort III (n = 51; DOB 1973–2016) did not receive NBS or special diet. The incidence of striatal degeneration in Cohorts I, II, and III was 7%, 47%, and 90%, respectively (p < .0001). No neurologic injuries occurred after 19 months of age. Among uninjured children followed prospectively from birth (Cohort I), measures of growth, nutritional sufficiency, motor development, and cognitive function were normal. Adherence to metabolic formula and L-carnitine supplementation in Cohort I declined to 12% and 32%, respectively, by age 7 years. Cessation of strict dietary therapy altered plasma amino acid and carnitine concentrations but resulted in no serious adverse outcomes. In conclusion, neonatal diagnosis of GA1 coupled to management with lysine-free, arginine-enriched metabolic formula and emergency IV infusions during the first two years of life is safe and effective, preventing more than 90% of striatal injuries while supporting normal growth and psychomotor development. The need for dietary interventions and emergency IV therapies beyond early childhood is uncertain.

1. Introduction

Glutaric acidemia type 1 (GA1; OMIM #231670) is a disorder of cerebral organic acid metabolism caused by biallelic variants of GCDH, which encodes a mitochondrial flavin-dependent glutaryl-CoA dehydrogenase (GCDH) that mediates degradation of lysine and tryptophan (Fig. 1). Neuronal GCDH deficiency results in proximal accumulation of glutaryl-coenzyme A (CoA) and its dicarboxylic acid derivatives, glutaric acid (GA) and 3-hydroxyglutaric acid (3HGA). These metabolites become concentrated in the brain due to its limited capacity to form 5-carbon carnitine and glycine conjugates from glutaryl-CoA [1,2] or export medium-chain dicarboxylates [3,4].

GCDH deficiency causes sudden degeneration of striatal neurons in at least 80% of untreated patients [5–8]. More than 90% of these
m values for SLC7A1 and arginine via a common facilitative transporter (SLC7A1) at the blood-brain barrier (BBB). Lysine and arginine have similar \( K_m \) values for SLC7A1 and compete for cerebral uptake within physiological concentrations ranges. The central nervous system (CNS) has a minimum lysine requirement for normal protein accretion and growth, lysine in excess of this requirement is normally oxidized via a GCDH-dependent degradation pathway. In GA1, the CNS produces glutaryl-CoA and its derivative dicarboxylic acids (glutarate and 3-hydroxyglutarate) in proportion to its rate of lysine uptake, which can be altered by competition with arginine at the BBB. The brain imports \( L \)-carnitine via one or more organic cation transporters (e.g., SLC22A5 and SLC22A4). In the mitochondrial matrix, acyltransferases theoretically drive the transfer of glutaryl moieties from glutaryl-CoA to \( L \)-carnitine to liberate free coenzyme A (CoA) and form glutaric carnitine, which can traverse multiple cellular barriers and be excreted. The quantitative importance of this 'detoxification' reaction in vivo is uncertain. The BBB is relatively impermeable to 5-carbon dicarboxylic acids and therefore the brain accumulates glutarate and 3-hydroxyglutarate to concentrations two to three orders of magnitude higher than those measured in plasma. These compounds exhibit a range of neurotoxic actions in cell culture and \( Gcdh^{-/-} \) mice.

encephalopathic crises strike during an infectious illness within the first 24 months of life but rarely occur without apparent provocation and may even happen in utero [9,10]. Regardless of their timing or mechanism, striatal lesions result in a complex extrapyramidal movement disorder that is the principal determinant of outcome. The predominant motor pattern observed is severe, generalized dystonia, which often may even happen in utero [9,10]. Regardless of their timing or mechanism of treatment (Table 1):

2. Patients and methods

2.1. Cohorts

The Institutional Review Board of Penn Medicine-Lancaster General Hospital approved the research protocol (2008–095-CSC) and parents consented in writing on behalf of their children. We studied a group of 168 individuals born with GA1 between August 1973 and October 2019 (current median age 11.8 years, range 0.2–43.6 years; 52% female), comprising 2276 patient-years of follow up and representing at least 41 different pathogenic \( GCDH \) allele combinations (Table S1). Ninety-one (54%) patients were homozygous for the c.1262C > T (p.Ala421Val) variant, 46 (27%) were homozygous or compound heterozygous for other \( GCDH \) alleles, and 31 (18%) had no molecular testing but a compelling clinical and biochemical GA1 phenotype, including elevated CSDC concentrations in plasma, elevations of both CSDC and 3HG in urine, congenital or infantile-onset macrocephaly, and characteristic middle cranial fossa fluid collections detected by magnetic resonance imaging [6,15].

For comparative analyses, we established three separate cohorts based on timing of diagnosis and method of treatment (Table 1):

Cohort I: 60 individuals (DOB 2006–2019) with GA1 were asymptomatic when identified between 0 and 14 days of age by one of two NBS methods (quantification of glutarylcarnitine [C5DC] from dried filter blood spots or detection of \( GCDH \) c.1262C > T from umbilical cord blood). After confirmatory biochemical and molecular testing, each child in Cohort I was treated consistently from birth to present (for patients < 2 years) or until ≥2 years of age using a standardized protocol that included a lysine-free, arginine-enriched (Lys−Arg+) metabolic formula (Glutarade, Nutricia North America), enteral \( L \)-carnitine (100 mg/kg•day) during illnesses (Table 2). For comparative analyses, we established three separate cohorts based on timing of diagnosis and method of treatment (Table 1):

Cohort II: 57 individuals (DOB 1989–2018) were identified by NBS and subsequently treated with emergency IV infusions during illness and a diet restricted to 1.0–1.3 g/kg•day of intact (i.e., ‘natural’) protein, but did not receive a lysine-free metabolic formula.

Cohort III: 51 individuals (DOB 1973–2016) were diagnosed with GA1 either during a workup for motor disability (90%) or incidentally through cascade testing; they did not have NBS or receive preventative therapies.

Data for Cohort I were collected prospectively to extend findings of a study initiated in 2006 to evaluate the safety and efficacy of a novel \( Lys^{-}Arg^{+} \) metabolic formula [16]. For Cohorts II and III, we conducted retrospective chart reviews to gather data about the method and timing of diagnosis, treatment strategy, neurologic outcome, and medical comorbidities.

2.2. Prospective treatment and monitoring protocol, cohort I (DOB 2006–2019)

2.2.1. Dietary therapy

Children in Cohort I (n = 60) were prescribed approximately equal quantities of intact protein (1.0–1.3 g/kg•day) and modified \( Lys^{-}Arg^{+} \) protein equivalent (1.0–1.3 g/kg•day) from birth to their present age (for those < 2 years) or at least two years of age (Table 2). The protein equivalent of \( Lys^{-}Arg^{+} \) metabolic formula was devoid of \( L \)-lysine, reduced in \( L \)-tryptophan (0.6%), and enriched with \( L \)-arginine (10.8%) as compared to protein in human milk (6.9% lysine, 1.8% tryptophan, 3.0% arginine) or commercial milk-based infant formulas (~9.1% lysine, 1.8% tryptophan, 3.0% arginine). The \( Lys^{-}Arg^{+} \) metabolic formula otherwise contained fat, carbohydrate, micronutrients, and all
other amino acids. Lys−Arg+ metabolic formula powder was available in two forms containing either 12% (Glutarade Junior) or 30% (Glutarade Essential) amino acids per dry powder weight, intended for use in younger versus older children, respectively. Both formulations had an energy content of 4 kcal per gram of dry powder.

Infants in Cohort I ingested 70–90 mg/kg/day of lysine, which is close to that of nursing babies (107 mg/kg/day), matches recommended safe intake (62–89 mg/kg/day), and exceeds the factorial estimate for normal growth (45–50 mg/kg/day) \cite{16,17}. Blending intact protein and Lys−Arg+ formula protein in a 1:1 ratio decreases the proportion of ingested lysine to arginine approximately four-fold, from 2.3–3.0 to 0.54–0.73 mg/mg (Table S2). L-arginine was not added to the diet as a separate supplement. L-carnitine (100 mg/mL) was dosed consistently at 100 mg/kg/day, rounded up to the nearest 0.5 mL increment.

After age two years, we recommended children with GA1 continue an enteral L-carnitine supplement (~1000 mg daily), observe a modest natural protein restriction (1.0–1.3 g/kg/day), and supplement their diet with lysine-free, arginine-enriched amino acids from Glutarade Essential (30% Lys−Arg+ amino acids per dry powder weight). However, the large majority of parents ultimately chose to disregard these recommendations, such that most individuals with GA1 had a fully unrestricted diet by seven years of age (see below).

2.2.2. Feeding strategy

Once daily, formula was prepared to a concentration and volume appropriate for age using components measured in milliliters, ounces, or grams (on a digital kitchen scale) (Table 3). In contrast to alternating nutritional sources throughout the day, we combined all components, including L-carnitine, into the same 24-h mixture. To allow for normal variation in both energy requirement and feeding behavior, infants were allowed to feed ad libitum according to their natural schedule within ±20% of the prescribed daily volume. When human milk was used as the source of intact protein, it was expressed, precisely measured, and added along with Lys−Arg+ powder and L-carnitine into the daily formula. Each child began a flexible transition to table foods between 6 and 14 months of age based on developmental cues. Table food was prescribed as average daily protein in grams (rather than milligrams) of lysine, allowing for ±15–25% variation day to day. We subtracted intact table food protein from the quantity in formula to maintain a total intact protein allocation of ~1 g/kg/day (Table 3). No children in Cohort I were fed via nasogastric or gastrostomy tube.

2.2.3. Emergency intravenous infusion therapy

We considered inpatient IV infusion therapy for any child who exhibited signs of an infectious illness or other serious medical condition. The decision to hospitalize was based on the perceived threat of encephalopathic crisis as influenced by age, feeding behavior, and the severity and duration of illness. Based on historical observations, we considered children to be at particularly high risk for brain injury if they were <24 months of age and had anorexia, gastroenteritis, or signs of any infectious illness lasting more than 1–2 days, even in the absence of fever. The standard inpatient protocol consisted of 10% dextrose in normal saline infused at 1.5-times the maintenance rate (glucose infusion 10–12 mg/kg/min), IV L-carnitine (100 mg/kg-dose) every 6–8 h (300–400 mg/kg/day), and supportive antiemetic, anti-pyretic, and antimicrobial agents as indicated (Table 2). Because dextrose, saline, and L-carnitine were consistently administered in parallel, we could not isolate the independent therapeutic role of each, and therefore refer to this combination simply as emergency IV infusion therapy.

2.2.4. Biochemical monitoring

Children on protocol were seen monthly in clinic during the first year of life and every two months during the second year of life (Table 2). Plasma amino acids were collected at each visit and the dietary proportion of intact to Lys−Arg+ protein equivalent was...
Table 2  
Cohort I (n = 60): Prospective Treatment and Monitoring Protocol.

<table>
<thead>
<tr>
<th>Clinical Context</th>
<th>Treatment Goals</th>
<th>Interventions</th>
<th>Monitoring Principles</th>
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</table>
| **Outpatient ‘Well Day’** | Normal growth trajectories  
Age-appropriate motor milestones  
Normal cognition and functional independence  
Prevention of nutritional deficiencies | Calories and micronutrients within age-appropriate DRIs  
Total protein: 2.0–2.6 g/kg/day  
• Intact (i.e., ‘natural’) protein: 1.6–1.8 g/kg/day  
• Lysine-free, arginine-fortified protein: 1.0–1.3 g/kg/day  
• Dietary ratio of lysine to arginine (mg/mg): 0.5  
• Lysine: 70–90 mg/kg/day  
• Tryptophan: 20–25 mg/kg/day  
L-carnitine (100 mg/mL): 100 mg/kg/day  
Formula concentration: 0.7–0.9 kcal/mL (20–27 kcal/or)  
Feeding schedule: *ad libitum*  
Standard immunizations | Outpatient visit schedule:  
• Birth to 1 year: once monthly  
• 1 to 2 years: every 2 months  
Plasma amino acid analysis each visit:  
• Lysine: 60–100 μmol/L  
• Lysine to arginine ratio (μmol/μmol): <1  
• Tryptophan: within normal reference range  
Plasma acylcarnitines for known or suspected non-adherence | |
| **Outpatient ‘Sick Day’** | Reduce intact protein intake by ~50%  
Increase lysine-free, arginine-fortified protein by ~50%  
Increase feeding frequency  
Control fever, nausea, and vomiting  
Treat identified infections  
Maintain frequent clinical contact  
**Triage to inpatient setting as indicated** | Calories and micronutrients within age-appropriate DRIs  
Total protein equivalent: 2.6–2.9 g/kg/day  
• Intact (i.e., ‘natural’) protein: 0.5–0.8 g/kg/day  
• Lysine-free protein: 1.5–1.8 g/kg/day  
• Dietary ratio of lysine to arginine (mg/mg): 0.2  
• Lysine: 35–45 mg/kg/day  
L-carnitine (100 mg/mL): 100 mg/kg/day  
Formula concentration: 0.7–0.9 kcal/mL (20–27 kcal/or)  
Feeding schedule: q3 hours around the clock  
Antimicrobials, antipyretics, and antiemetics as indicated | Physical examination: assess status, identify source of illness  
Phone and/or outpatient follow-up at least every 12 hours  
**Triage to inpatient setting if:**  
• Decreased formula intake  
• Vomiting and/or diarrhea  
• Unrelenting fever  
• Persistent or worsening illness  
• Treatment non-adherence | |
| **Inpatient ‘Emergency’ Therapy** | Rapidly initiate IV therapy  
Continuous IV saline and dextrose infusion  
High-dose IV L-carnitine  
Reduce intact protein intake by ~50%  
Increase lysine-free, arginine-fortified protein by ~50%  
Control fever, nausea, and vomiting  
Treat underlying infections as indicated  
Ensure smooth transition to enteral ‘Well Day’ diet | Replace fluid deficit by (repeated) IV saline bolus as indicated  
Dextrose 10% in normal saline: 1.5x maintenance requirement  
L-carnitine IV: 100 mg/kg/dose every 6 hours  
‘Sick Day’ formula: *ad libitum* as tolerated  
Antimicrobials, antipyretics, and antiemetics as indicated | Laboratory studies at admission:  
• Glucose, general chemistries, and complete blood count  
• Repeat POC glucose and laboratory studies as indicated  
Temperature and vital signs every 6–8 hours  
Neurologic assessment every 6–8 hours  
Strict quantification of total fluid intake and output  
Daily weight tracking | |

*a* For routine vaccinations, we administer ‘Sick Day’ diet plan in the outpatient setting for 24–48 h.

*Abbreviations*: DRI, dietary reference intake, National Institutes of Health (https://ods.od.nih.gov/HealthInformation/Dietary_Reference_Intakes); IV, intravenous; POC, point-of-care.
To evaluate the long-term safety of Lys−Arg+ metabolic formula, we designed a custom Excel spreadsheet (Microsoft Corporation) to estimate cerebral uptake of circulating amino acids during the first two years of life [16]. Briefly, a group of three cationic amino acids (lysine, arginine, ornithine) compete for entry into the brain via a common facilitative transporter (SLC7A1; a.k.a. CAT1, y++) [19,20] which is saturated under physiological conditions, such that cerebral influx of each SLC7A1 substrate is influenced by ambient plasma concentrations of its competitors. Competition is expressed by an apparent \( K_{\text{app}} \) called \( K_{\text{app}} \) (μmol/L), calculated for each amino acid according to the equation:

\[
K_{\text{app}} = K_{m} \left[ 1 + \sum_{i=n}^{n} \left( \frac{C_{i}}{K_{i}} \right) \right]
\]

(1)

where \( K_{m} \) is the classical Michaelis-Menten affinity constant for the single amino acid of interest, \( C_{i} \) is the plasma concentration (μmol/L) for each of \( n \) competitors, and \( K_{i} \) is the classical affinity constant of that competitor (μmol/L). For a given plasma amino acid profile, \( K_{\text{app}} \) values were determined for each SLC7A1 substrate using empirically-derived Michaelis-Menten constants [21]. The \( K_{\text{app}} \) value was then used to estimate the brain influx (nmol per minute per gram of brain tissue) of each amino acid in the competing group, according to the equation:

\[
\text{Influx} = \frac{V_{\text{max}} (C)}{(K_{\text{app}} + C)}
\]

(2)

where \( V_{\text{max}} \) and \( C \) are the maximal transport velocity (nmol/min·g) and plasma concentration (μmol/L), respectively, of each amino acid [22]. Estimated brain influx values were compared to those calculated from a pediatric control population (\( N = 52 \)) and depicted as standard scores (i.e., z-scores), where \( z = \frac{[\text{study subject value} - \text{control mean}]}{\text{control standard deviation}} \). All cerebral uptake values represent calculated heuristics and should not be interpreted as direct measurements of amino acid flux. An analogous method was used to estimate brain uptake of zwitterionic amino acids (glutamine, histidine, isoleucine, leucine, methionine, phenylalanine, threonine, tryptophan, tyrosine, and valine) that compete for entry into the brain via the SLC7A5 transporter [21].

### 2.4. Statistics

Statistical calculations were performed using Prism 8 software (https://www.graphpad.com). Kaplan-Meier analyses were applied to outcomes of stratal degeneration, death, and time to motor milestone acquisition. The two-sided Fisher’s exact test was used to calculate relative risk of brain injury in Cohorts II and III as compared to Cohort I. Normal reference plasma amino acid concentrations were derived from 52 non-fasted healthy children without disorders of amino or organic acid metabolism and converted to z-scores for graphical representation [16]. Developmental trajectories of GA1 patients were compared with those of healthy siblings using Mann-Whitney and logrank Mantel-Cox tests. The two-tailed Student’s t-test was used to compare SB-5 scales between GA1 subjects and their age-matched sibling controls. Paired vital signs before and 18–36 h into IV infusion therapy were compared using the Wilcoxon signed-rank test. To investigate differences among three or more groups, we used one-way analysis of variance (ANOVA) followed by the Tukey post-test for pairwise comparisons. Most continuous data sets (e.g. plasma amino acid concentrations and concentration ratios) were not normally distributed, and thus their central tendency is reported as the median and 25th to 75th interquartile range (IQR) except where otherwise noted.

### 3. Results


##### 3.1.1. Diagnosis

Forty-one (68%) children in Cohort I were homozygous for GCDH c.1262C > T (p.Ala421Val). For 17 of them, this risk for GA1 was
known prenatally and molecular testing of umbilical cord blood in our CLIA-certified molecular laboratory yielded a definitive diagnosis at a median of one (range 0–4) postnatal day(s). Among 43 remaining patients in Cohort I, dried filter paper blood spots were collected at a median of 2 (range 0–5) postnatal days and results were reported through state NBS at a later median age of 8 (range 5–14) days (p < .0001). The median diagnostic filter paper C5DC concentration was 1.15 (IQR 0.88–1.78) μmol/L and the minimum was 0.42 μmol/L (normal reference value < 0.27 μmol/L). In Pennsylvania, NBS included reflex tier two testing for the GCDH c.1262C  >  T variant. We encountered no false negative or false positive screening results at our center between 1994 and present.

3.1.2. Dietary therapy

For each child in Cohort I, we analyzed an average of 18 diets prescribed between birth and two years of life (1061 dietary formulations in total). Calories represented in milk sources and medical food closely matched estimated energy expenditure until ~12 months of age, after which unmeasured calories from table foods increased (Fig. 2a). The median diagnostic filter paper CSDC concentration was 1.15 (IQR 0.88–1.78) μmol/L and the minimum was 0.42 μmol/L (normal reference value < 0.27 μmol/L). In Pennsylvania, NBS included reflex tier two testing for the GCDH c.1262C > T variant. We encountered no false negative or false positive screening results at our center between 1994 and present.

3.1.3. Outpatient biochemical monitoring, birth to two years

We collected and analyzed a total of 1054 plasma amino acid samples in the outpatient setting from children in Cohort I; 855 of these were obtained during the first two years of life under conditions of strict dietary adherence (average of 14 per subject and one per visit). Here, we define a ‘strict’ diet as one in which intakes of both intact and lysine-free protein were reliably known and the prescribed and ingested volume of Lys−Arg+ metabolic formula closely aligned. The ‘relaxed’ diet applies to older children on a recommended but unquantified (typically higher) range of intact protein, whose intake of metabolic formula often fell short of the recommended volume.

A strict Lys−Arg+ diet was associated with median plasma lysine and arginine concentrations of 80 (IQR 60–100) μmol/L and 98 (IQR 80–115) μmol/L, respectively (Fig. 3a), and a median plasma Lys/Arg

---

**Fig. 2.** Cohort I: Dietary variables from Birth to 24 Months. (A) For the first 12 months of life, average prescribed calories from formula (red circles, ± 1SD) closely matched estimated energy requirement (EER) as determined by the doubly-labeled water method (DLW; https://www.nap.edu/), shown as a blue dotted line. Unmeasured calories from table foods increase during the second year of life. (B) Intact protein (gray diamonds) and lysine-free, arginine-enriched amino acids from metabolic formula (Lys−Arg+; red circles) were prescribed in approximately equal quantities throughout the first two years of life. (C) After ~8 months of age, the proportion of intact protein from table food (gray) as compared to milk sources (red) increased. (D) The average enteral L-carnitine supplement was ~100 mg/kg/day (red line) and at no time decreased to < 50 mg/kg-day (gray circles).
The average ratio of lysine to arginine in plasma (Lys/Arg) was ≤1.0 on strict diet (red circles, mean, ± 1SD) but increased as adherence to both intact protein recommendations and metabolic formula intake became more relaxed after age two years (blue diamonds). Most GA1 subjects older than 7 years (gray triangles) no longer restricted their natural protein intake or used Lys−Arg+ metabolic formula and their plasma Lys/Arg ratios increased to the normal control range (gray shading, median and IQR, ****p < .0001). The gray shaded area represents estimated cerebral lysine uptake (median and IQR) calculated from plasma amino acid profiles of 52 healthy children without GA1. Age on the abscissa is depicted as a log10 scale with a vertical dashed line at age two years. (D) For children ≤2 years of age on a strict Lys−Arg+ diet, lysine (red circles) and arginine (blue circles) had the lowest and highest adjusted cerebral uptake values, respectively, depicted here as z-scores (gray shading represents the normal z-score range of −2 to +2). Calculated brain uptake values for all other SLC7A1 and SLC7A5 substrates (gray circles), including tryptophan, were within the normal reference range. (Table 4) and no child in Cohort I developed signs of tryptophan or niacin deficiency (i.e. pellagra) [23].

Serum folate concentration exceeded the limit of quantitation (> 20 ng/mL) in children taking Lys−Arg+ metabolic formula; those on supplemental L-carnitine had elevated total and free plasma carnitine levels (p < .0001). Other laboratory indices of nutritional sufficiency and general health were within normal reference intervals (Table S3). Plasma tryptophan values were within the normal range (Table 4) and no child in Cohort I developed signs of tryptophan or niacin deficiency (i.e. pellagra) [23].

3.1.4. Dietary adherence
All Cohort I subjects remained on a strict diet using Lys−Arg+ metabolic formula until two years of age. Dietary adherence decreased steadily thereafter, so that the probability of a child remaining on Lys−Arg+ metabolic formula after age seven years was only 12% (Fig. 4a). Cessation of diet was associated with a higher median plasma lysine concentration and Lys/Arg ratio (Table 4, Fig. 3b). Similarly, only 32% of GA1 subjects remained on an L-carnitine supplement after age six years. Plasma free and total carnitine decreased markedly as a consequence but we observed no overt clinical signs of carnitine deficiency (Fig. 4b).

3.1.5. Hospitalizations
There were 153 recorded hospitalizations for children in Cohort I. During the first two years of life, each child was hospitalized a median...
of three (range 0–14) times and 85% of children were hospitalized at least once for emergency IV therapy. The median age of hospitalization was 12.6 months for the main indications of gastroenteritis (44%), respiratory tract infection (32%), fever without an identified source (16%), and acute otitis media (5%). Each hospitalization lasted a median of two (1–8) days.

For children in Cohort I, Table 5 lists vital signs and select laboratory values recorded at the time of admission and again an average of 24 (18–36) hours into the course of emergency IV therapy. Two-thirds of patients admitted to the hospital before age two years had objective signs of inflammation indicated by elevated body temperature (> 38 °C, 100.4 °F) and/or a serum C-reactive protein concentration > 8.0 mg/dL. These two variables were modestly correlated (rs = 0.42, p < .0001). Average body temperature did not change during the first 18–36 h of hospitalization (p = .620). Heart rate and blood pressure were generally within the normal range at the time of admission and decreased 2.4–7.0% during IV therapy (p < .0001).

Laboratory studies collected at the time of admission did not show metabolic acidosis or hypoglycemia; this was true even in two patients who presented with acute striatal necrosis. The mean presenting serum total carbon dioxide and anion gap were 22 ± 3 (range 13–29) mmol/L and 11 ± 3 (range 5–21) mmol/L, respectively, and only two children (1.3%) presented with a serum total carbon dioxide concentration < 16 mmol/L. The average presenting serum glucose concentration was 95 ± 22 (range 47–202) mg/dL; only four values (2.6%) were < 60 mg/dL and these were not associated with signs of neuroglycopenia or metabolic stroke. For more than 90% of hospitalizations, blood was collected only at the time of admission. For the few subjects who had at least one repeat set of laboratory studies (n = 14), average serum glucose increased in response to IV dextrose, but this result was not significant (p = .143) due to broad variation (−17% to +174%) among a small number of samples. No child developed hypoglycemia sufficient to warrant insulin therapy.

There were no serious adverse events associated with dextrose...
infusions of 9–12 mg/kg•min or L-carnitine doses ≤400 mg/kg•day, which were administered exclusively by peripheral (as opposed to central) vein. No child developed motor regression while receiving emergency IV therapy.

3.2. Clinical outcomes in cohorts I-III

3.2.1. Psychomotor outcomes

The incidence of striatal degeneration in Cohorts I, II, and III was 7%, 47%, and 90%, respectively (\(p < .0001\)) (Fig. 5a). Newborn screening decreased the relative risk of striatal degeneration 7-fold (\(p < .0001; 95\% CI 3\text{-} to 19\text{-}fold, p < .0001\)) and, when coupled to the use of \(\text{Lys}^{-}\text{Arg}^+\) metabolic formula, 14-fold (95%CI 6- to 35-fold, \(p < .0001\)) (Table 1). No neurologic injuries occurred after 19 months of age.

The proportion of striatal lesions that presented as acute encephalopathic crisis versus insidious motor delay was 84% before the advent of NBS (Cohort III) and 50% in the modern NBS era (Cohort I). Children with insidious motor delay tended to have better functional outcomes as compared to those who presented with acute motor regression. In Cohort I, two children were rendered mute, non-ambulatory, and fully disabled after suffering acute striatal necrosis; two additional children from this cohort had infantile-onset hypotonia and dystonia but no witnessed encephalopathic crisis. They learned to crawl (12.5 and 13 months) and walk independently (24 months) and now enjoy a high degree of self-efficacy.

All 91 subjects with GA1 who were spared neurologic injury are alive and well at a mean follow up of 9.6 ± 8.3 (range 0.2–43.4) years. Uninjured children from Cohort I (\(n = 56\)) who took \(\text{Lys}^{-}\text{Arg}^+\) metabolic formula grew normally during the first two years of life (Fig. 6). They achieved independent sitting (5–9 months) and crawling (8–11 months) as expected relative to their unaffected siblings (Fig. 7a-d), but walked about two months later, at a median of 14 as compared to 12 months (\(p = .045\)). First articulate words were similarly delayed about two months (\(p = .036\)). Ten subjects from Cohort I who were old enough for cognitive testing (5–12 years) scored similar to their age-matched control siblings on FSIQ and SB-5 subscales (Fig. 7e).

3.2.2. Mortality and comorbidity

Across cohorts, a total of 77 patients suffered brain injury (Cohort I, \(n = 4\); Cohort II, \(n = 27\); Cohort III, \(n = 46\)). Post-mortem and neuroimaging studies consistently showed bilateral neuronal loss and gliosis of the lentiform nuclei in a dorsolateral to ventromedial gradient ranging from mild to severe (Fig. 8a). Eighteen patients with striatal lesions were lost to clinical follow up. Of the 59 remaining, 24% (\(n = 14\)) died from complications of dystonia at a median age of 14.5 (range 2.5–39.1) years (Fig. 5b). Medical and surgical comorbidities were common among survivors; most became wheelchair-dependent

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<thead>
<tr>
<th>Vital signs</th>
<th>Mean ± SD (Range)</th>
<th>Mean ± SD (Range)</th>
<th>Relative change</th>
<th>Wilcoxon P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature, °C</td>
<td>37.4 ± 0.8 (34.9–40.6)</td>
<td>37.5 ± 0.9 (36.1–39.9)</td>
<td>0.10%</td>
<td>0.620</td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>134 ± 16 (100–188)</td>
<td>130 ± 13 (86–170)</td>
<td>–2.4%</td>
<td>0.018</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>110 ± 13 (81–145)</td>
<td>104 ± 11 (80–134)</td>
<td>–4.6%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>65 ± 12 (41–90)</td>
<td>58 ± 9 (42–88)</td>
<td>–7.0%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table 5

Cohort I: Measurements at the Time of Hospital Admission and 18–36 Hours Into IV Infusion Therapy (\(n = 153\) Hospitalizations).

Abbreviations: C, Celsius; na, not available; SD, standard deviation.


Fig. 5. All Cohorts: Clinical Outcomes. (A) The incidence of striatal degeneration in Cohorts I (blue solid line), II (gray dotted line), and III (red dashed line) was 7%, 47%, and 90%, respectively (\(p < .0001\)) (Fig. 5a). Newborn screening decreased the relative risk of striatal degeneration 7-fold (\(p < .0001; 95\% \text{CI 3-} \text{to 19-fold, } p < .0001\)) and, when coupled to the use of \(\text{Lys}^{-}\text{Arg}^+\) metabolic formula, 14-fold (95%CI 6- to 35-fold, \(p < .0001\)) (Table 1). No neurologic injuries occurred after 19 months of age.

The proportion of striatal lesions that presented as acute encephalopathic crisis versus insidious motor delay was 84% before the advent of NBS (Cohort III) and 50% in the modern NBS era (Cohort I). Children with insidious motor delay tended to have better functional outcomes as compared to those who presented with acute motor regression. In Cohort I, two children were rendered mute, non-ambulatory, and fully disabled after suffering acute striatal necrosis; two additional children from this cohort had infantile-onset hypotonia and dystonia but no witnessed encephalopathic crisis. They learned to crawl (12.5 and 13 months) and walk independently (24 months) and now enjoy a high degree of self-efficacy.

All 91 subjects with GA1 who were spared neurologic injury are alive and well at a mean follow up of 9.6 ± 8.3 (range 0.2–43.4) years. Uninjured children from Cohort I (\(n = 56\)) who took \(\text{Lys}^{-}\text{Arg}^+\) metabolic formula grew normally during the first two years of life (Fig. 6). They achieved independent sitting (5–9 months) and crawling (8–11 months) as expected relative to their unaffected siblings (Fig. 7a-d), but walked about two months later, at a median of 14 as compared to 12 months (\(p = .045\)). First articulate words were similarly delayed about two months (\(p = .036\)). Ten subjects from Cohort I who were old enough for cognitive testing (5–12 years) scored similar to their age-matched control siblings on FSIQ and SB-5 subscales (Fig. 7e).

3.2.2. Mortality and comorbidity

Across cohorts, a total of 77 patients suffered brain injury (Cohort I, \(n = 4\); Cohort II, \(n = 27\); Cohort III, \(n = 46\)). Post-mortem and neuroimaging studies consistently showed bilateral neuronal loss and gliosis of the lentiform nuclei in a dorsolateral to ventromedial gradient ranging from mild to severe (Fig. 8a). Eighteen patients with striatal lesions were lost to clinical follow up. Of the 59 remaining, 24% (\(n = 14\)) died from complications of dystonia at a median age of 14.5 (range 2.5–39.1) years (Fig. 5b). Medical and surgical comorbidities were common among survivors; most became wheelchair-dependent

Fig. 5. All Cohorts: Clinical Outcomes. (A) The incidence of striatal degeneration in Cohorts I (blue solid line), II (gray dotted line), and III (red dashed line) was 7%, 47%, and 90%, respectively (\(p < .0001\)). In 168 patients managed over a span of three decades, no brain injuries were observed after age 19 months (gray shaded area). Note divided abscissa. (B) Striatal lesions were a risk factor for untimely death (red dashed line; median survival 39 years, \(p = .0024\)). All 91 patients who escaped neurologic injury are alive and functionally independent (gray solid line).
procedures were posterior spinal fusion and proximal femoral varus derotation osteotomy and/or pelvic osteotomy (Fig. 8d). During the postoperative period, pain and anxiety often exacerbated dystonia in a self-reinforcing cycle, sometimes escalating to life-threatening status dystonicus.

4. Discussion

4.1. Pathophysiology and prevention of striatal degeneration

The GCDH-deficient brain accumulates glutaryl-CoA, GA, and 3HGA proportional to its rate of lysine uptake [27,28], which is highest during embryonic life and early infancy [29,30]. Studies in cell culture and transgenic Gcdh−/− mice reveal the potential for these compounds to activate excitotoxic cascades, amplify oxidative stress, inhibit respiratory complexes, depress sodium-potassium ATPase activity, and disrupt the maturation and function of astrocytes [31–39]. One or more of these mechanisms might precipitate striatal degeneration, but none fully explain its temporal and histological selectivity. The maturation of medium spiny neurons must also play a role, rendering them uniquely vulnerable to histotoxins during a circumscribed phase of development [40,41].

Neuroimaging studies indicate how this biochemical state might affect the developing brain. Asymptomatic infants with GA1 have reduced fluorodeoxyglucose uptake in the lentiform nuclei, reduced cerebral blood flow (CBF), and signs of cerebrovascular congestion [9,42] that coincide with normal developmental surges of synaptogenesis, excitatory neurotransmission, substrate utilization, and perfusion [43–45]. As this normal developmental sequence unfolds, medium spiny neurons in the striatum—with their unique constellation of channels, receptors, and enzymes [40]—potentially experience a mismatch between energy supply and demand during a time when they are unusually sensitive to excitotoxic and oxidative forms of injury [46–48].

Based on the foregoing model, protecting the striatum from GCDH deficiency is predicated on minimizing its exposure to neurotoxins during a discrete phase of development [41]. In principle, this is accomplished by manipulating dietary amino acid content to reduce cerebral lysine influx while administering L-carnitine to clear glutaryl-CoA from brain cell mitochondria (Fig. 1, [16,27,49–51]). The provision of ‘emergency’ therapy in the form of IV dextrose and saline is intended to stabilize energetically fragile brain tissue during intervals of physiologic stress [41].

Beginning in 1989 [52,53], NBS allowed us to detect pre-symptomatic Amish babies with GA1 and decrease their risk of neurologic injury from 90% (Cohort III) to 47% (Cohort II), representing a seven-fold reduction of relative risk. The use of Lys−Arg+ metabolic formula in Cohort I further reduced the incidence of striatal degeneration to just 7% (14-fold reduction of relative risk) [16]. Our experience aligns closely with that of Boy et al., who found that NBS for GA1 in Germany reduced the incidence of neurologic injury from > 90% to 36% and, when coupled to lysine-restricted diet, to 7% [54]. Taken together, these data show that: (1) the neuroprotective effects of emergency IV therapy and Lys−Arg+ metabolic formula are additive; (2) metabolic formulas devoid of lysine might be to some degree interchangeable; (3) similar outcomes can be expected in cohorts that differ with regard to the distribution of pathogenic GCDH genotypes; and (4) the same basic elements of therapy can be deployed in various settings to comparable effect.

4.2. Elements of effective therapy

Newborn screening with tandem mass spectrometry (TMS) detects GA1 with a sensitivity and specificity of at least 93% and 99%, respectively [15,55,56]. In certain populations like the Amish, targeted allele detection enables molecular diagnosis within hours of life [12].
but this strategy does not appear to improve outcome over standard TMS-based methods with ~8-day turnaround. Pre-symptomatic diagnosis not only reduces the risk of neurologic impairment but also its potential severity. In the absence of NBS for GA1, ~85% of striatal lesions present as acute, pan-striatal cytotoxic edema that culminates in extensive neuronal loss, generalized dystonia, and profound functional impairment (Cohort III). In the post-screening era, ~50% of children with striatal degeneration present with insidious motor delay; the
associated brain lesions are typically confined to the dorsolateral putamen, visible months or years before a conspicuous movement disorder, and predictive of a better functional outcome [9,10].

Following the diagnosis of GA1 by NBS, use of a metabolic formula devoid of lysine and enriched with arginine establishes desired plasma amino acid concentrations ranges that can be maintained throughout the transition from formula to table foods. Because transport $K_m$ values for lysine ($K_m = 70 \mu\text{mol/L}$) and arginine ($K_m = 56 \mu\text{mol/L}$) at the blood-brain barrier are similar [21], they exhibit meaningful transport competition within concentration ranges induced by Lys−Arg+ metabolic formula. Based on our calculations, dietary management with Lys−Arg+ formula could decrease the brain’s toxin exposure by as much as 40% during its vulnerable phase of development, but this also has potential to interfere with normal brain growth [57–59]. Mindful of this risk, we monitor infants with GA1 every month. In general, those who adhere to a strict therapeutic diet during the first two years of life exhibit normal growth, achieve developmental milestones on time, and have normal cognitive function later in childhood. Other investigators report similar outcomes, supporting the overall safety of current GA1 treatment guidelines [60–63].

Rigid insistence on many aspects of feeding may not be necessary to ensure good outcome, provided medical food is balanced appropriately with other dietary components and offered ad libitum. We ask parents to quantify all dietary ingredients but allow them to combine these once daily into a single mixture, which they offer in rhythm with each baby’s natural appetite and feeding cues. Following the transition to table foods, metabolic control can be maintained while also allowing for some flexibility (e.g., ± 20%) in daily protein intake. Outpatient monitoring is streamlined around just three parameters—physical growth, psychomotor development, and the plasma Lys/Arg ratio.

As long as diet conforms to accepted guidelines [63,64] and is adjusted for incremental weight gain, normal development can be achieved with minimal or no specialized biochemical testing. Indeed, several families from Cohort I lived in geographically remote, resource-limited households and were unable to adhere to the demanding clinical monitoring schedule. In between a more limited number of outpatient visits, parents collected accurate growth measurements at home and communicated these to our clinical team in a way that allowed their children to have timely dietary adjustments and excellent neurologic outcomes.

There remains some controversy about the appropriate duration of prescription dietary therapy. In our experience over three decades, no neurological crises occurred after age 19 months, but the true window of striatal vulnerability remains unknown. In one large international cross-sectional study ($n = 279$), 95% of all brain injuries occurred before age 24 months but one was reported at 70 months. This unusual case is often cited to support the recommendation for strict dietary management until age six years [63,64]. Mindful of the potential for long term complications, we advise that GA1 patients > 19 months remain on dietary therapy. Nevertheless, most choose to quit diet of

![Fig. 8. Morbidity. (A) An axial brain section from a deceased GA1 patient shows characteristic atrophy of the striatum in a dorsolateral to ventromedial gradient (left hemisphere, red shading). A normal age-matched brain is shown for comparison (right hemisphere, blue shading). (B) Striatal lesions typically cause severe, generalized dystonia. (C) The large majority of patients with dystonia require one or more orthopedic surgeries to address common musculoskeletal complications such as scoliosis and hip dislocation. (D) A radiograph of the left hip shows the femoral head (red shading) dislocated from the acetabulum (blue dotted line) in an adolescent with GA1.](image-url)
their own accord (Fig. 4A). Although we observed no overt consequences of dietary non-adherence through adolescence and early adulthood, we recognize this might lead to complications later in life (see below).

4.3. Knowledge gaps

Intravenous infusion of dextrose, saline, and L-carnitine during illness is a widely accepted treatment strategy for GA1 [52,63,64]. We know very little about how this intervention protects the brain, but it is empirically successful; throughout 153 hospitalizations we attended over three decades, no GA1 patient developed neurologic regression while on inpatient IV therapy. With regard to the efficacy of IV infusions, timing matters. Emergency IV therapy need not and should not be delayed to accommodate transport to a tertiary academic center; the infusion protocol can be safely administered at almost any hospital with basic pediatric services. Over the years, we have successfully collaborated with community hospitals throughout the United States to establish convenient, affordable, and timely access to emergency IV therapy for children with GA1.

Pathophysiological concepts that inform IV therapy continue to evolve. Following its initial discovery, GA1 was viewed as an episodic intoxication syndrome in which systemic proteolysis generates circulating neurotoxins that cross the blood-brain barrier to poison the brain [52,65]. According to this paradigm, infusion of dextrose and saline were intended to suppress generation of organic acids and clear them from the bloodstream [6]. We now know this reasoning to be incorrect for a number of reasons: (1) ambient plasma concentrations of GA and 3HGA in patients are much lower than histotoxic concentrations in vitro [33,66,21]) acute metabolic acidosis is seldom observed during catabolic states (9, 3) under all conditions, plasma GA and 3HGA are orders of magnitude below concentrations measured in brain tissue [67,68]; and (4) 5-carbon dicarboxylates do not readily cross the blood-brain barrier [3,69]. Finally, the most compelling evidence comes from experimental Gcdh−/− mice, which only develop central nervous system intoxication in response to excess dietary lysine [27,28].

Over the last 15 years, attention has shifted to the possibility that dextrose-containing saline infusions somehow stabilize metabolically vulnerable neurons, perhaps by improving their substrate supply [9,42]. This would require that IV therapy augment cerebral glucose delivery by increasing one or both of its determinants: plasma glucose concentration and CBF. Contrary to this idea, we found that infusing glucose in saline at 10–12 mg/kg/min does not reliably increase plasma glucose concentration, nor does it impact hemodynamics in a way that should alter CBF, as indicated by similar blood pressure measurements before and after the initiation of emergency IV therapy.

Like emergency IV infusion, L-carnitine supplementation is a widely accepted practice that lacks a strong evidence base [63,64,70]. Beyond its obvious role in correcting systemic deficiency, treatment with L-carnitine is founded on the premise that it crosses the blood-brain barrier, gains access to the mitochondrial matrix of neurons, and drives an acyltransferase reaction with glutaryl-CoA [2,71]. The human brain imports L-carnitine via a number of sodium-coupled transporters (e.g., SLC22A5 and SLC22A4; https://www.proteinatlas.org/) and, based on \( K_m \) values measured in rat brain slices (1920–2850 \( \mu \text{mol/L} \)) [72,73], a five-fold increase in plasma carnitine should increase its cerebral uptake by a comparable degree. However, the activity of neuronal carnitine acyltransferases toward 5-carbon dicarboxylate thioesters appears to be quite low [71,74] and the quantitative relevance of mitochondrial ‘detoxification’ in vivo thus remains unclear.

4.4. Challenges and opportunities

Prior to the advent of TMS-based NBS in the United States, most neurologic injuries from GA1 were catastrophic in nature. We now have neuroprotective therapy that is safe, simple, and highly effective [75–78] but only a minority of developed nations currently screen for GA1 [75]. Among 46 patients in Cohort III with striatal lesions, more than 85% were Gross Motor Function Classification System (GMFCS) level V, requiring a wheelchair for mobility and retaining limited or no ability to maintain a seated or standing posture, control limb movements, speak, or swallow [79]. When using a disability weighting consistent with severe functional impairment [80] and accounting for the attendant increase in mortality, these data suggest that in the absence of a systematic newborn screening and treatment program, each child born with GA1 loses an average of 64 disability-adjusted life years.

The economic impact of NBS for GA1 is also considerable. In developed nations, aggregate direct, indirect, and social costs of caring for an individual with GMFCS V level disability is between $46,000 and $64,000 per annum (corrected to 2016 U.S. dollars). Considering a 39-year median survival for disabled GA1 patients, this extrapolates to a lifetime cost of between US$1.8 and 2.5 million per brain-injured individual. Recognizing both the social and economic implications [64], the U.S. Health Resources and Service Administration includes GA1 as a recommended condition for universal newborn screening for all babies born in the United States and allied territories (https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html).

Although important evidence gaps remain, current protocols prevent more than 90% of brain injuries and are unlikely to face competing strategies in the near future. A rough power calculation shows why; to be proven superior, any novel intervention needs to be tested in parallel against a cohort of equal size managed according to the current standard of care [63,64]. A statistically meaningful difference between 93% and 97% efficacy would require at least 250 infants in each treatment group. Given the potentially grave neurologic consequences of such a randomization, it would pose a serious ethical challenge and most parents would be reluctant to participate.

4.5. Treatment of GA1 beyond early childhood

A strong confluence of evidence from multiple sources now supports the use of dietary therapy to prevent striatal degeneration from GCDH deficiency. In contrast, only scattered and conflicting data inform treatment of GA1 beyond early childhood. The natural age-related decline in treatment adherence brings this problem into sharp focus (Fig. 4A). In patients aged 8 to 71 years, symptoms and signs attributed to GA1 have included headache, nausea, nystagmus, gaze palsy, hyperreflexia, syncope, vertigo, epilepsy, ataxia, tremor, dysmetria, dysarthria, memory impairment, incontinence, orofacial dyskinesia, confusion, dementia, and peripheral neuropathy [81–86]. Unfortunately, none of these clinical phenomena are specific to GA1 and no combination of them has coalesced into a distinctive late onset neurological ‘phenotype’ of GA1. In at least half of GA1 subjects without striatal lesions, magnetic resonance images (MRI) reveal abnormal signals in white matter tracts and deep extrastriatal nuclei [61,81,87]. These likely reflect areas of interstitial edema and vacuolization [9,28,67,68,88–91], but it is not known how such changes correspond to neurological function or if they change in response to dietary treatment.

A similar consideration applies to the potential for non-neurological complications of GA1. For example, reports from experimental animals and humans indicate that GA1 might confer susceptibility to both acute [92–94] and chronic forms of kidney disease [95]. In Cohort I, we observed no signs of renal insufficiency among patients ≤3 years of age (mean serum creatinine 0.27 ± 0.06, range 0.20–0.40 mg/dL; Table 5) and, over the last three decades, had no GA1 patient present with overt renal failure. However, chronic renal insufficiency could go undetected among subjects from Cohorts II and III, for whom we have limited longitudinal renal biomarker data. It is important to reiterate, however, that the presence of a disease process, renal or otherwise, does not assure its response to therapy. The nephropathy of methylmalonic
acidemia (MMA) provides an instructive example; there is no indication that progression of kidney disease in MMA is altered by dietary therapy [96].

The possibility of late-onset disease complications must be balanced against the fact that individuals with GA1 can remain healthy well into adulthood after living decades with no specific therapy. Among 91 individuals we studied without striatal lesions, 59% ranging from 2.6 to 43.6 years of age are off prescription medical foods and 52% stopped L-arginine. Fourteen of them are > 17 years, have been off protein restriction and dietary supplements since early childhood, and report no clinically significant neurological problems or health concerns. Similar stories emerge from false positive NBS results that reveal GCDH deficiency in otherwise healthy mothers [56,83,97,98].

The foregoing discussion should not be misinterpreted as a formal recommendation to stop dietary therapy for GA1 patients older than two years. Rather, we intend only to draw attention to a problem in need of more evidence. To this end, future clinical research should target two related but distinct questions: (1) Is it possible to more sharply define ‘non-striatal’ complications of GCDH deficiency after age two years, and consolidate these into something like a canonical late-onset GA1 phenotype that can be reliably anticipated, measured, and tracked in a clinical setting?; and (2) If such a phenotype becomes established, can its natural course be altered by standard dietary therapies (e.g., lysine-restriction and/or enteral L-carnitine)? Separating these ideas is critically important, because the mere existence of a rational therapy does not guarantee its effectiveness [59].

Over the long term, patients’ willingness to adhere to dietary therapy should improve if it can be linked to meaningful outcomes. In the absence of such associations, however, we recognize the potential for prolonged but unnecessary therapy to foster stigmatization, maladaptive relationships, and mental distress—a phenomenon termed the ‘vulnerable child syndrome’, which can have serious long-term psychological consequences [59]. Balancing the potential risks and benefits of treatment for GA1 beyond early childhood therefore represents an ongoing quandary open to new research, and marks a pressing challenge for clinical investigators.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2020.09.007.

References


