Nutrition Management of Glutaric Acidemia Type 1

19

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Contents

Core Messages

- Glutaric acidemia type 1 (GA-1) is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan metabolism.
- A defect of glutaryl-CoA dehydrogenase results in the accumulation of 3-hydroxyglutaric acid and glutaric acid.
- Nutrition management of GA-1 consists of restricting lysine and tryptophan, supplementing L-carnitine, and providing sufficient energy to prevent catabolism.
- Patients with GA-1 have a particularly high risk of permanent cerebral damage from a metabolic crisis.

19.1 Background

Glutaric acidemia type 1 (GA-1) is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan metabolism caused by a deficiency of glutaryl-CoA dehydrogenase (Fig. 19.1).

GA-1 results in the accumulation of 3-hydroxyglutaric acid and glutaric acid in the urine [1, 2], the metabolites most likely associated with the risk of neurological damage (Box 19.1).

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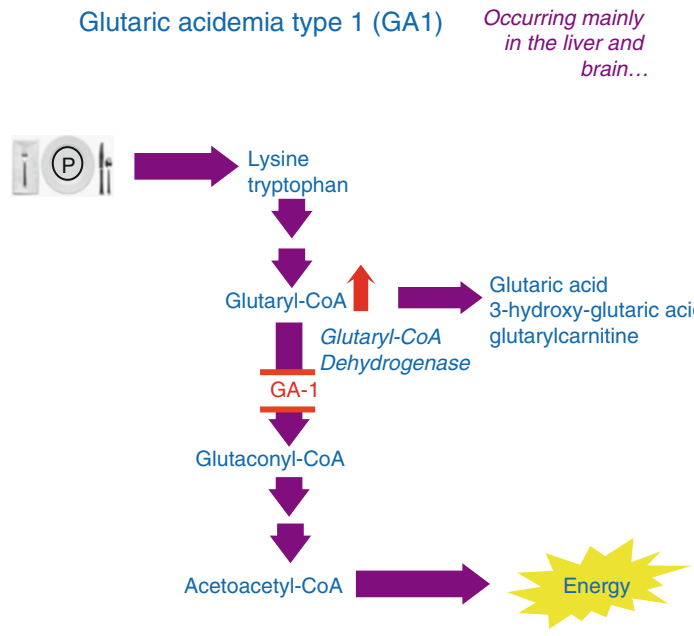

Fig. 19.1 Metabolic pathway of glutaric acidemia type 1 (GA-1)

Box 19.1: Principles of Nutrition Management in GA-1

Restrict: Lysine and tryptophan

Supplement: L-carnitine, riboflavin[a], pantothenic acid[a]

Toxic metabolites: 3-hydroxyglutaric acid and glutaric acid[b]

[a]Practice varies – supplemented in some clinics.

[b]These metabolites accumulate but concentrations are not related to patient outcomes.

However, they have not been reliable when used to assess patient outcomes [3].

The management of GA-1 poses several challenges: (1) metabolic decompensations are associated with a very high risk of permanent neurological insult in GA-1; (2) good biomarkers to guide therapy have not been identified; and (3) there is a lack of agreement about how long strict dietary treatment is necessary. The risk for neurological damage appears to be greatest in newborns and early childhood, when cerebral lysine uptake is the highest [1, 2]. There are no published reports of acute encephalopathic crises in children over age 6 years, but there are documented cases of chronic neurological deterioration in patients with late-onset disease without crises [4]. Diet management using medical food and protein restriction rather than treatment with a protein restriction alone may be advisable [4, 5]. Many clinics continue to recommend a less stringent, but lifelong, dietary treatment despite the current understanding of the efficacy of the diet after age 6 years. A further description of the diagnosis and management of GA-1 is described in Chap. 18.

19.2 Nutrition Management

19.2.1 Chronic Nutrition Management

Expanded newborn screening allows for early diagnosis of GA-1 that leads to timely, preventive

Table 19.1
Recommended daily intake for a patient with GA-1 [1, 4, 8]

Age	Protein[a] (g/kg)	Lysine[a] (mg/kg)	Tryptophan[a] (mg/kg)
Birth to 6 months	2.75–3.5	65–100	10–20
6 months to 1 year	2.5–3.25	55–90	10–12
1 year to 4 years	1.8–2.6	50–80	8–12
4 years to 7 years	1.6–2.0	40–70	7–11

Energy, vitamin,* and mineral intakes should meet the DRI and normal fluid requirements
*Some clinics recommend supplemental riboflavin (100 mg/day) and pantothenic acid (400–600 ug/kg/day)
[a]These are average ranges. Adjustments should be made based on growth, laboratory findings and health status

Box 19.2: Initiating Nutrition Management in an Asymptomatic Infant with GA-1

Goal: Prevent neurological insult associated with metabolic crises.

Step-by-step:

1. Establish intake goals based on clinical status and laboratory values.

Intake goals

Age (days)	Protein [1] (g/kg)	Lys [1, 8] (mg/kg)	Lysine/arginine ratio [8]	Carnitine [8] (mg/kg)	Riboflavin[a] [10] (mg)	Pantothenate[b] [8] (μg/kg)
5	2.75–3.5	65–100	1:1.5–1:2	75–100	100	400–600

2. Calculate the amount of infant formula/breast milk[c] needed to meet lysine needs.
3. Determine the amount of protein provided by the whole protein source.
4. Calculate the amount of medical food required to meet remaining total protein needs (Fig. 19.2).
5. Calculate arginine provided by whole protein and GA-1 medical food to ensure lysine-to-arginine ratio is correct. Supplement arginine if needed.
6. Determine the calories provided by both the whole protein source and GA-1 medical food. Provide the remaining calories from a protein-free medical food.
7. Determine the amount of fluid required to make a formula that provides 20–25 kcal/oz (depending on energy needs and volume tolerated).

[a]Some clinics supplement riboflavin. Administer 15–25 mg mixed into 3–4 feedings per day for maximum absorption [10].
[b]May not be supplemented by all clinics. Check individual clinical protocols for guidance.
[c]In severe forms, expressed breast milk is recommended.

management, thereby reducing the risk of acute neurological damage associated with untreated GA-1 [3]. Minimizing the risk of cerebral damage and maintaining normal development and growth are the overarching goals of the nutrition management of GA-1 [6, 7]. The most critical component of nutrition management in patients with GA-1 is the prompt treatment of intercurrent illnesses. L-carnitine supplementation is also an integral component of management.

The diet for a patient with GA-1 is restricted in the amino acids lysine and tryptophan. The goals for nutrient intake are provided in Table 19.1. When well, the patient with GA-1 has normal requirements for most other nutrients, including energy, vitamins, and minerals (Box 19.2). Medical foods free of lysine and tryptophan are used to meet protein goals (Fig. 19.2). These medical foods provide varying amounts of essential amino acids, fat,

	Arginine (mg)	Tryptophan (mg)	Carnitine (mg)	Energy (kcals)
GlutarAde™ Essential[a]	1082	60	10	154
GlutarAde™ Junior[a]	1080	60	30	410
GlutarAde™ AA Blend[a]	1072	60	30	40
Glutarex®-1[b]	1033	0	600	320
Glutarex®-2[b]	1033	0	600	136.6
GA-1 Anamix® Early Years[a]	874	0	0.01	350
XLysXTrpMaxamaid®[a]	890	0	0	130
XLysXTrpMaxamum®[a]	880	0	0	76
GA Gel™[c]	830	60	11	81
GA Express™[c]	815	63	11	49.5
GA™[d]	688	0	0	331

[a]Nutricia North America (Rockville MD; nutricia-na.com)
[b]Abbott Nutrition (Columbus OH; abbottnutrition.com)
[c]Vitaflo USA (Alexandria,VA; vitaflousa.com)
[d]Mead Johnson Nutrition (Evansville IN; meadjohnson.com)

Fig. 19.2 Comparison of medical foods for GA-1 (per 10 g protein)

carbohydrate, vitamins, and minerals as well as L-arginine. In the dietary management of GA-1, it is important to note that there is less tryptophan in whole protein than lysine (on a molar basis); therefore, restricting lysine may cause an over-restriction of tryptophan. Blood concentrations of both amino acids require close monitoring (Sect. 19.3).

Arginine competes with lysine for uptake across the blood-brain barrier and should be provided at 1.5–2 times that of dietary lysine. Strauss et al. [8] recommend providing measured amounts of both arginine and lysine at the same time as the key to efficacy [8]. Reports of improved outcomes in patients consuming a diet providing the recommended lysine-to-arginine ratio have been published, although brain concentrations of these amino acids have not been quantified [8].

Standard infant formula or breast milk provides lysine and tryptophan during infancy. Due to the risk of neurological consequences associated with energy deprivation and catabolism, close monitoring of intake and appropriate weight gain is crucial in all infants. In breastfed infants, weight gain is the primary measure of caloric adequacy. Solid foods that are naturally low in protein (lysine) may be introduced when developmentally appropriate for the child and specialty low protein foods may be used to provide sufficient energy and variety to the diet. Providing sufficient energy can be challenging in patients with GA-1. Those who have sustained cerebral damage usually present with severe dystonia and choreoathetosis, interfering with the patient's ability to eat normally. If severe enough, the patient may require a gastrostomy tube [7]. Energy needs may be increased in patients with dystonia [9] or decreased in patients who are nonambulatory [7].

Monitoring the ratio of lysine to arginine concentrations in the blood, as well as in the diet, may also prove to be a useful strategy when treating patients with GA-1.

L-carnitine supplementation is routinely provided to patients with GA-1 as a way to reduce intramitochondrial glutaryl-CoA and provide extracellular release without the synthesis of glutaric acid and 3-hydroxyglutaric acid. L-carnitine conjugates with coenzyme A esters to form acylcarnitines. The typical L-carnitine dose is 75–100 mg/kg/day or sufficient quantities to maintain free L-carnitine concentrations within the normal range [4]. Large doses of enteral L-carnitine may cause loose stools or diarrhea [11]. In the hospitalized patient with acute illness, a continuous infusion of intravenous L-carnitine is preferably provided.

Glutaryl-CoA dehydrogenase is a riboflavin-dependent enzyme that converts glutaryl-CoA to glutaconyl-CoA. Once the diagnosis is confirmed, a trial of pharmacological doses of riboflavin (100–200 mg/day) may be successful in lowering glutaric acid or 3-hydroxyglutaric acid in some patients with specific responsive mutations [12]. Results range from neurological improvement and reduced urinary glutaric acid excretion in one patient [12] to a reported 20 % increase in residual activity of glutaryl-CoA dehydrogenase [13]. Some centers recommend routine riboflavin supplementation regardless of response. Many preparations of riboflavin are distasteful and cause staining due to the bright orange color of the vitamin [8, 13]. High doses of riboflavin have been reported to cause gastric distress. The recommended regimen is to provide 15–25 mg of riboflavin three to four times per day with food for maximum absorption [10], but some have reported starting patients on 50–100 mg, twice per day.

19.2.2 Acute Nutrition Management

Sick-day protocols for home use are used extensively for many inherited metabolic diseases, including organic acidemias, but the practice is different with GA-1. The risk for neurological injury is highest during illnesses with reduced energy intake, fever, and associated catabolism. Very aggressive treatment and a zero tolerance with regard to hospital admission during any of these presentations can help prevent permanent neurological damage. Thus, if a patient has an illness in which he or she is not consuming adequate energy due to vomiting, poor intake, or diarrhea and/or if the patient has a fever (>38.5 °C), it is considered a medical emergency and the patient must be seen in the emergency department immediately. The consequences of an acute metabolic crisis are dire and include irreversible neurologic sequalae involving damage to the basal ganglia (striatal necrosis), which can cause a normally developing infant or child to have a lifetime of severe physical and developmental disabilities. During an illness that is associated with catabolism, maintaining usual therapy ("well-day" diet) and supplementing L-carnitine is NOT sufficient to prevent an acute crisis; additional nonprotein energy sources must be provided. Management of a sick-day diet at home must be done with the guidance of the metabolic physician, and the threshold for seeking emergency treatment is very low, even for relatively minor illnesses, particularly during the first 6 years of vulnerability. Sick-day management includes reducing natural protein intake, continuing consumption of a lysine and tryptophan-free medical food, and providing extra sources of protein-free energy (e.g., Pro-Phree®, Duocal®, SolCarb®, Polycal®) (Box 19.3). The L-carnitine dose is often increased as well.

Sick-day management is difficult to do at home; the key is in reducing whole protein intake, providing sufficient L-carnitine, and consuming enough energy to prevent catabolism. All patients with GA-1 should have a written emergency department protocol that can be referenced if the patient is seen at a hospital unfamiliar with the management of GA-1. In such cases, the patient's metabolic physician should be contacted and consulted regarding management. Acute medical management must

Box 19.3: "Sick-day" Nutrition Management of a Patient with GA-1

This diet may be used at home for minor illnesses. If the patient does not improve over a relatively short period of time or if energy intake is inadequate, it is considered a medical emergency in GA-1.

	Children's Hospital Colorado[a]	Strauss [8]
Energy	110–120 % of usual intake	95–115 kcal/kg
Whole (natural) protein (g/kg/day)	0.6–0.7	0.5
Lysine-free medical food (g/kg/day)	Maintain current	1.5–2.0
L-carnitine[b] (mg/kg/day)	50	100

[a]Children's Hospital Colorado, GA-1 IMD Clinic protocol; please check your clinic's protocol.

[b]Use caution in diarrheal illnesses.

Box 19.4: Transitioning a Hospitalized Patient with GA-1 from a "Sick-Day" to a "Well-Day" Diet

1. Introduce the sick-day diet (Box 19.3) as soon as the child can tolerate feedings, initially given in combination with IV dextrose to meet energy goals.
2. Wean IV dextrose[a] as formula intake approaches maintenance well-day diet volume.
3. Transition gradually to well-day formula to provide at least half of the protein/lysine intake, starting within 24–36 h after admission.
4. Gradually transition to full intake of the well-day formula prescription before discharge.

[a]See Appendix J

commence quickly to avoid catabolism and includes discontinuing protein feeds for 24–36 h, providing sufficient energy intake, and managing the underlying illness. When admitted to the emergency room, intravenous glucose such as glucose 10 % at 1.5 times maintenance and Intralipid® (Baxter Healthcare, Deerfield, IL) at 2 g/kg/day are often rapidly added, particularly for children with compromised oral intake due to illness. Cessation of the essential amino acid lysine should be limited in duration since its deficiency will induce catabolism resulting in adverse effect. Thus, usually within 24–36 h of cessation of protein feeds, the patient can begin to transition whole protein feeds back to his or her usual diet (Box 19.4).

19.3 Monitoring

Laboratory markers that are good indicators of the clinical status of patients with GA-1 are lacking. While there is no direct relationship between excretion of glutaric acid and 3-hydroxyglutaric acid and patient outcomes, some clinics may consider increases in the concentration of 3-hydroxyglutaric acid or glutaric acid as warning signs of changes in health status and may elect ongoing monitoring of such metabolites.

Nutritional monitoring includes ensuring adequate growth and nutrient intake, especially markers of protein status (Chap. 7). Monitoring plasma amino acids is necessary to ensure that concentrations of the essential amino acids,

Box 19.5: Nutrition Monitoring of a Patient with GA-1

- Routine assessments including anthropometrics, dietary intake, and physical findings (Appendix F)
- Laboratory monitoring
  - Diagnosis specific
    - 3-hydroxyglutaric acid (urine)
    - Glutaric acid (urine)
    - Carnitine (total, free, esterified)
    - Plasma amino acids, including:
      - Lysine
      - Arginine
      - Tryptophan
- Nutrition laboratory monitoring of patients on lysine and/or protein-restricted diets may include markers of:
  - Protein sufficiency[a]
  - Nutritional anemia (hemoglobin, hematocrit, MCV, serum vitamin B_{12} and/or methylmalonic acid (MMA), total homocysteine, ferritin, iron, folate, total iron binding capacity)
  - Vitamin and mineral status (25-hydroxyvitamin D, zinc, trace minerals)
  - Others as clinically indicated

[a]Further described in Chap. 7.

lysine and tryptophan, are maintained within the normal range for age (based on the metabolic laboratory's reference ranges) (Table 19.2).

Care must be taken to avoid essential amino acid deficiencies, particularly tryptophan. Tryptophan is difficult to quantify using certain methodologies [14]. Serum albumin binds tryptophan, with one binding site per albumin molecule. Variable albumin binding may make free tryptophan concentrations variable [14]. The frequency of monitoring depends on the patient's age and health status. During early infancy, many clinics measure plasma amino acids along with anthropometrics each week (Box 19.5).

19.4 Summary

The nutrition management of GA-1 presents a clinical challenge because the benefit of a lifelong lysine and tryptophan-restricted diet is not established; there are no good biomarkers to guide treatment decisions; and acute metabolic crises can result in striatal damage causing irreversible neurological sequelae. Preventing acute metabolic crisis is the primary goal of treatment. Lysine-restricted, arginine-supplemented diets are believed to offer some benefit perhaps by altering the flux of lysine and arginine across the blood-brain barrier. L-carnitine conjugates and removes glutaric acid and 3-hydroxyglutaric acid from the body and is a key part of therapy.

Table 19.2 Plasma concentration reference ranges for arginine, lysine, and tryptophan for patients with GA-1

Amino acid	0–1 month	1–24 months	2–18 years	Adult
Arginine (μmol/L)	6–140	12–133	10–140	15–128
Lysine (μmol/L)	92–325	52–196	48–284	100–250
Tryptophan (μmol/L)	–	5–60	34–47	42–106

Reference ranges for Children's Hospital Colorado; check your laboratory for reference ranges

19.5 Diet Calculation Example for an Infant with GA-1

Example: Infant with GA-1

Patient information	Nutrient intake goals (per day)
Ten (10) day old infant male weighing 3.2 kg who was diagnosed with GA-1 based on elevated 3-OH glutaric acid concentrations. Patient is asymptomatic and eating well. Current intake is 19 oz of Enfamil per day	**Lysine:** 70 mg/kg (range: 65–100 mg/kg) **Tryptophan:** 10–20 mg/kg **Protein:** 3.0 g/kg **Energy:** 125 kcal/kg (range: 95–145 kcal/kg) Recommended caloric density of formula: 20–22 kcal/oz

Select nutrient composition of products used in GA-1 diet calculation example (using standard infant formula as the source of whole protein)

Medical food/formula	Amount (g)	LYS (mg)	ARG (mg)	TRP (mg)	Protein (g)	Energy (kcal)
GA-1 Anamix® Early Years[a]	100	–	1,180	–	13.5	473
Enfamil® Premium Powder[b]	100	750	240	163	10.6	510

[a]Nutricia North America (Rockville, MD)
[b]Mead Johnson Nutrition (Evansville, IN)

Diet prescription summary for diet calculation example (using standard infant formula as the source of whole protein)

Medical food/formula	Amount (g)	LYS (mg)	ARG (mg)	TRP (mg)	Protein (g)	Energy (kcal)
GA-1 Anamix® Early Years[a]	47	–	555	-	6.3	222
Enfamil® Premium Powder[b]	30	224	72	49	3.2	153
Total per day		224	627	49	9.5	375
Total per kg		70	196	15	3.0 (1.0 g/kg of natural protein)	117

[a]Nutricia North America (Rockville, MD)
[b]Mead Johnson Nutrition (Evansville, IN)
Values rounded to nearest whole number for amount of formula powder, Lysine, Arginine, Tryptophan, and Energy. Values rounded to the nearest 0.1 g for protein

Step-by-Step Diet Calculation

Step 1. Calculate the amount of Lys required each day.

Lys goal × Infant Weight = mg Lys per day

70 mg/kg Lys × 3.2 kg = 224 mg/day Lys

Step 2. Calculate the amount of standard infant formula needed to meet the daily Lys requirement.

Amount of Lys required per day ÷ mg of Lys in standard infant formula.

224 mg/day ÷ 750 mg Lys = 0.30

0.30 × 100 g = 30 g standard infant formula needed to meet daily Lys requirement

Step 3. Calculate protein and energy provided from standard infant formula.

Amount of standard infant formula × protein provided in 100 g of standard infant formula.

0.30 × 10.6 g protein = 3.2 g protein in standard infant formula

Step 4. Calculate amount of protein to fill the diet prescription.

Protein goal × Infant weight = daily protein requirement

3.0 g protein × 3.2 kg = 9.6 g daily protein requirement

Daily protein requirement – protein provided by standard infant formula

9.6 g − 3.2 g = 6.4 g protein needed from Lys/Trp-free medical food to fill in the diet prescription.

Step 5. Calculate the amount of Lys/Trp-free medical food required to fill protein requirement.

Protein needed from Lys/Trp-free medical food ÷ protein in 100 g of medical food.

6.4 g ÷ 13.5 g protein in Lys/Trp-free medical food = 0.47 g

0.47 g × 100 g = 47 g Lys/Trp-free medical food required to fill the diet prescription.

Step 6. Calculate the total energy provided from standard infant formula and Lys/Trp-free medial food.

Amount of standard infant formula × kcal in 100 g of standard formula.

0.30 g × 510 kcal = 153 kcal

Amount of Lys/Trp-free medical food × kcal of 100 g of Lys/Trp-free medical food.

0.47 g × 473 kcal = 222 kcals

Add standard infant formula + Lys/Trp free medical food for total kcal provided in diet prescription.

153 kcal + 222 kcal = 375 total kcal

375 kcal ÷ 3.2 kg = 117 kcal/kg

Step 7. Calculate the final volume of the formula to make a concentration of approximately 20–22 kcal per ounce.

Amount of total calories provided by diet prescription ÷ 20 fluid ounces = number of ounces of formula needed to provide caloric concentration of 20 kcal/oz.

375 kcal ÷ 20 kcal/oz = 18.75 oz of formula

(Note: If final volume prescribed is 19 oz, caloric concentration will be 19.7 kcal/oz; if final volume prescribed is 18 oz caloric concentration will be 20.8 kcal/oz- either is acceptable)

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