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GUIDELINES

Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision

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Abstract Glutaric aciduria type I (GA-I; synonym, glutaric acidemia type I) is a rare inherited metabolic disease caused by deficiency of glutaryl-CoA dehydrogenase located in the catabolic pathways of L-lysine, L-hydroxylysine, and L-tryptophan. The enzymatic defect results in elevated concentrations of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and glutaryl carnitine in body tissues, which can be reliably detected by gas chromatography/mass spectrometry (organic acids) and tandem mass spectrometry (acylcarnitines). Most untreated individuals with GA-I experience acute encephalopathic crises during the first 6 years of life that are triggered by infectious diseases, febrile reaction to vaccinations, and surgery. These crises result in striatal injury

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References to electronic databases: Glutaric aciduria type I: OMIM no. 231670. Glutaryl-CoA dehydrogenase: EC 1.3.8.6

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and consequent dystonic movement disorder; thus, significant mortality and morbidity results. In some patients, neurologic disease may also develop without clinically apparent crises at any age. Neonatal screening for GA-I us being used in a growing number of countries worldwide and is cost effective. Metabolic treatment, consisting of low lysine diet, carnitine supplementation, and intensified emergency treatment during catabolism, is effective treatment and improves neurologic outcome in those individuals diagnosed early; treatment after symptom onset, however, is less effective. Dietary treatment is relaxed after age 6 years and should be supervised by specialized metabolic centers. The major aim of this second revision of proposed recommendations is to re-evaluate the previous recommendations (Kölker et al. J Inherit Metab Dis 30:5-22, 2007b; J Inherit Metab Dis 34:677-694, 2011) and add new research findings, relevant clinical aspects, and the perspective of affected individuals.

Abbreviations

AA	Amino acids
AAM	Amino acid mixture
C5DC	Glutarylcarnitine
DBS	Dried blood spots
GA	Glutaric acid
GA-I	Glutaric aciduria type I
GCDH	Glutaryl-CoA dehydrogenase
GC/MS	Gas chromatography/mass spectrometry
GRADE	Grading of recommendations, assessment, development and evaluation
GDG	Guideline development group
IU	International unit
MRI	Magnetic resonance imaging
MS/MS	Tandem mass spectrometry
NBS	Newborn screening
3-OH-GA	3-Hydroxyglutaric acid
SDH	Subdural hemorrhage
SIGN	Scottish intercollegiate guidelines network

Introduction

Glutaric aciduria type I (GA-I, OMIM no. 231670) is an autosomal recessive metabolic disorder of lysine metabolism with an estimated worldwide incidence of 1:110.000 (Lindner et al. 2004; Kölker et al. 2007a). Primarily a neurologic disorder GA-I is considered a cerebral organic aciduria caused by deficiency of glutaryl-CoA dehydrogenase (GCDH, EC 1.3.8.6). Recent publications, however, have challenged this view, demonstrating that the peripheral nervous system (Herskovitz et al. 2013) and kidneys might also be involved in the long-term disease course (Kölker et al. 2015b). The *GCDH* gene is mapped to chromosome 19p13.2 and encodes a flavin adenine dinucleotide-dependent mitochondrial matrix protein that is involved in degradation of L-lysine, L-hydroxylysine, and L-tryptophan (Fu et al. 2004; Greenberg et al. 1995). So far, 187 (confirmed or likely) pathogenic mutations have been published and are listed in the *Human Gene Mutation Database* (data drawn on 18 April 2016; Goodman et al. 1998; Zschocke et al. 2000). Biochemically, GA-I is characterized by accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC). These metabolites can be detected in body fluids [urine, plasma, cerebrospinal fluid (CSF)] and tissues using gas chromatography/mass spectrometry (GC/MS) or electrospray-ionization tandem mass spectrometry (ESI-MS/MS; Baric et al. 1999; Chace et al. 2003). Two arbitrarily defined biochemical subgroups of individuals have been described based on urinary metabolite excretion of GA: low and high (Baric et al. 1999). Low excreters mostly carry missense mutations on at least one *GCDH* allele, resulting in a residual enzyme activity of up to 30 % (Busquets et al. 2000; Goodman et al. 1998). Both subtypes show a similar clinical course and a high risk of developing striatal injury if untreated (Christensen et al. 2004; Kölker et al. 2006). A recent neuroradiologic study revealed a high frequency of white-matter abnormalities progressing with age and increased intracerebral concentrations of GA and 3-OH-GA detected in vivo by proton magnetic resonance spectroscopy [^{1}H-MRS] in high excreters (Harting et al. 2015). However, clinical relevance of these observations remains to be determined.

Since the description of two index patients in 1975 (Goodman et al. 1975), more than 500 individuals with GA-I have been reported worldwide. Five genetic isolates are known showing a high carrier frequency (up to 1:10) and incidence (up to 1:250): the Amish Community in Lancaster County, PA, USA (Morton et al. 1991), the Oji-Cree First Nations in Manitoba and Western Ontario, Canada (Haworth et al. 1991), the Irish Travellers in the Republic of Ireland and UK (Naughten et al. 2004), the Lumbee Indian Tribe in North Carolina, USA (Basinger et al. 2006), and the Xhosa and other subgroups of the South African black population (van der Watt et al. 2010).

In neonates and infants, unspecific neurologic symptoms such as muscular hypotonia and delayed motor development occur in about half of all individuals with GA-I, whereas others are asymptomatic. Macrocephaly is a frequent (75 %) but nonspecific finding and is present at or shortly after birth (Bjugstad et al. 2000; Renaud 2012). Considering a 3 % frequency of macrocephalic individuals in the general population, the positive predictive value (PPV) of macrocephaly for GA-I is low. Untreated, 80-90 % of infants will develop neurologic disease during a vulnerable period of brain development (mostly between ages 3 and 36 months, with individual

reports until age 72 months) following an acute encephalopathic crisis. Such crisis is often precipitated by intercurrent febrile illness, febrile reaction to vaccinations, or surgical intervention (Hoffmann et al. 1991; Kölker et al. 2006). The characteristic neurologic sequela of these crises is acute bilateral striatal injury and, subsequently, a complex movement disorder. Morbidity and mortality is high in these individuals (Kyllerman et al. 2004; Kölker et al. 2006). In contrast, long-term prognosis for individuals diagnosed early is promising, although mortality rates are not yet available, as newborn screening only began in the late 1990s.

Two further clinical-onset types have been described: individuals with *insidious onset* type develop neurologic disease and striatal injury in the absence of encephalopathic crises (Busquets et al. 2000; Hoffmann et al. 1996). Although the frequency of this disease variant is supposed to be about 10–20 % of symptomatic individuals (Kölker et al. 2006), studies demonstrate higher frequencies in some populations (Busquets et al. 2000; Strauss et al. 2007). Furthermore, insidious onset in newborn screening cohorts has been observed in individuals not adhering to current dietary recommendations (Heringer et al. 2010). Notably, insidious onset in one of the five genetic cohorts has vanished following improvement of dietary management (Strauss et al. 2011; Kölker et al. 2012). Individuals with *late onset* form can present with nonspecific neurologic symptoms such as headaches, vertigo, transient ataxic gait, reduced fine motor skills, or fainting after exercise but do not develop striatal injury. Periventricular white-matter changes are the prominent finding on brain magnetic resonance imaging (MRI) (Bähr et al. 2002; Külkens et al. 2005). However, it remains unclear whether this proposed subgroup should be regarded as its own entity. Of note, single cases of neoplastic brain lesions in untreated individuals with late-onset disease (Herskovitz et al. 2013; Korman et al. 2007; Pierson et al. 2015) and in one adult (Burlina et al. 2012) have been reported. However, whether these findings are coincidental or whether adults with GA-I have an increased risk of (brain) neoplasms—as in L-2-hydroxyglutaric aciduria, another cerebral organic aciduria (Patay et al. 2012)—has not been clarified. Frequency of epilepsy is increased in patients with GA-I, and seizures might even be the initial clinical presentation (Kölker et al. 2015a; McClelland et al. 2009; Young-Lin et al. 2013; Zaki et al. 2014). As a first extracerebral manifestation, a recent study reported an increased frequency of chronic renal failure in affected adults (Kölker et al. 2015b), which has also been demonstrated in a mouse model for GA-I (Thies et al. 2013).

During the last three decades, therapeutic goals have been established and optimized. Analogous to other organic acidurias, dietary treatment in combination with supplementation orally of L-carnitine (maintenance treatment) and an intensified emergency treatment during episodes of intercurrent illness, are the mainstay of treatment and have considerably reduced the frequency of acute encephalopathic crises and movement disorders (now 10–20 % from 80–90 %) and, subsequently, morbidity and mortality in individuals who are diagnosed early (Boy et al. 2013; Couce et al. 2013; Heringer et al. 2010; Kölker et al. 2006, 2007a; Monavari and Naughten 2000; Strauss et al. 2003, 2007, 2011; Viau et al. 2012).

GA-I is therefore considered to be a treatable condition. However, no characteristic or pathognomonic sign or symptoms occurring before encephalopathic crisis are known, making early clinical diagnosis difficult. Since C5DC can be detected in dried blood spots (DBS) by MS/MS-based newborn screening (NBS) and early therapy is effective, GA-I has been included in many national NBS panels (Loeber et al. 2012) which has been proven to be a cost-effective diagnostic strategy (Pfeil et al. 2013).

Although outcome in GA-I has improved over the last two decades, differences still exist in disease diagnosis and management. The major aim of this second revision of recommendations is to re-evaluate previous guideline recommendations (Kölker et al. 2007b, 2011) and formulate revised and–for new topics–new recommendations for diagnosis and management based on the best evidence available, relevant clinical experience, and perspectives of affected individuals.

Methods

Guideline development

The guideline development process was initiated in 2003 and first published in 2007 (Kölker et al. 2007b). The first guideline revision was published 4 years later (Kölker et al. 2011) based on results of a prospective follow-up study evaluating the clinical impact of guideline recommendations. It has been shown that adherence to therapeutic recommendations significantly improves the outcome in individuals with GA-I diagnosed by NBS (Heringer et al. 2010), a positive result confirmed in another cohort (Strauss et al. 2011). This second revision is based on result of a guideline development group (GDG) meeting on 27 November 2015 in Heidelberg, Participation comprised 15 international experts in metabolic medicine, neuropediatrics, clinical biochemistry, nutrition, neuroradiology, and psychology, as well as one representative of a support group for affected individuals (Glutarazidurie e.V.). In addition, the GDG received feedback from international external experts. An overview of all 17 recommendations and statements of this second revision is given in Table 1.

Table 1 Summary of second-revision recommendations and statements

Recommendation (R)/Statement (S)		Level of recommendation according to SIGN[a]
Diagnostic procedures		
R1	When GA-I is suspected, diagnostic workup, development of treatment plans, appropriate information, and training for affected individuals and their families should take place in a specialized metabolic center. Affected individuals should be transferred to such centers without delay.	Strong recommendation for
R2	Positive NBS result and suggestive clinical, biochemical, and/or neuroradiologic signs should be confirmed by diagnostic workup including quantitative analysis of GA and 3-OH-GA in urine and/or blood and mutation analysis of *GCDH* gene and/or GCDH enzyme analysis in leukoyctes or fibroblasts (Fig. 1).	Strong recommendation for
S1	Maternal GA-I should be included in the differential diagnoses if NBS shows: (1) decreased free carnitine or (2) increased C5DC but diagnostic confirmation in the child is negative or no other adequate explanation for initially abnormal screening results can be found.	–
R3	In children with SDH (including suspicion of shaken baby syndrome) and/or bitemporal fluid collections suggesting frontotemporal hypoplasia and/or arachnoid cysts, a diagnostic workup using the algorithm for targeted diagnostic workup (Fig. 1) is strongly recommended.	Strong recommendation for
S2	SDH is usually found in combination with other neuroradiologic abnormalities characteristic for GA-I (i.e., frontotemporal hypoplasia, enlarged CSF spaces, etc., Suppl. Table 3). Isolated SDH without these characteristic abnormalities per se is not suggestive of GA-I and should not result in targeted diagnostic workup.	-
Metabolic maintenance treatment		
R4	Metabolic treatment and regular follow-up monitoring should be implemented by an interdisciplinary team in a specialized metabolic center.	Strong recommendation for
S3	There is no evidence for a clinical benefit of high-dose arginine supplementation orally for maintenance treatment or for the use of arginine IV for emergency treatment. For this reason, arginine intake should only be provided by lysine-free, tryptophan-reduced, arginine-containing AAM and natural protein within a balanced low-lysine diet.	–
R5	Low-lysine diet with additional administration of lysine-free, tryptophan-reduced mixtures containing essential amino acids is strongly recommended for dietary treatment up to age 6 years.	Strong recommendation for
R6	After age 6 years, dietary treatment should follow an age-adapted, protein-controlled protocol based on safe levels for protein intake. Dietary changes should be accompanied by regular dietary advice.	Recommendation for
R7	L-carnitine should be supplemented lifelong aiming to maintain normal plasma concentration of free L-carnitine.	Recommendation for
Emergency treatment		
R8	It is strongly recommended to start emergency treatment without delay and to perform it aggressively during febrile illness, febrile reactions to vaccinations, or perioperative management within the vulnerable period for striatal injury (up to age 6 years).	Strong recommendation for
R9	Emergency treatment in children after age 6 years should be considered during severe illness or perioperative management and performed similarly to that in the age group 0–6 years with individual adaptation.	Recommendation for research
Neurologic complications		
R10	Neurologic (i.e., epilepsy, movement disorder) or neurosurgical (SDH) complications should be managed by a neuropediatrician (later neurologist) and/or neurosurgeon in close cooperation with the metabolic specialist.	Strong recommendation for
Monitoring		
R11	Therapeutic effectiveness should be monitored by regular follow-up and intensified at any age if symptoms progress, new symptoms manifest (disease- or therapy-related), or nonadherence to treatment recommendations is suspected. For clinical endpoints of monitoring, see recommendations 13–17.	Strong recommendation for
R12	Individuals with GA-I should be admitted to a hospital and closely monitored after head trauma.	Recommendation for

Table 1 (continued)

Recommendation (R)/Statement (S)		Level of recommendation according to SIGN[a]
R13	Analysis of urinary concentrations of GA and 3-OH-GA should not be used for treatment monitoring.	Recommendation for
R14	Infants and children on a low lysine diet should have amino acids in plasma (ideally 3–4 h postprandially) quantified regularly. Concentrations of lysine and other essential amino acids should be maintained within the normal range.	Strong recommendation for
R15	Carnitine level in plasma should be monitored regularly in all individuals with GA-I.	Recommendation for
R16	Neuroradiological investigation should be performed if signs of neurologic deteroriation occur.	Recommendation for
R17	Neuropsychologic functions, i.e., intelligence/developmental quotient, motor functions, and language should be evaluated regularly to detect specific deficits early and allow for initiation of appropriate intervention services.	Recommendation for
S4	Psychosocial effects of diagnosis and treatment of GA-I should be assessed in both affected individuals and their families as part of routine monitoring.	–

SIGN Scottish Intercollegiate Guidelines Network, *C5DC* glutarylcarnitine, *GCDH* glutaryl-CoA dehydrogenase, *CSF* cerebral spinal fluid, *SDH* subdural hemorrage, *AAM* amino acid mixture, *GA* glutaric acid, *3-OH-GA*3-hydroxyglutaric acid, *GA-I* glutaric aciduria type I

[a] Level of recommendation is only provided for recommendations (R); evidence base for statements (S) is limited, but the guideline development group considered them essential to good clinical practice

Consensus procedure

Relevant key questions were identified by interdisciplinary consensus procedure comprising the recommendations of the first revision (Kölker et al. 2011) and new key questions arising since then. To achieve formal consensus, a structured consensus process with neutral moderation was chosen. All key questions were systematically discussed by the GDG. For each recommendation, the level of achieved consensus (and of recommendation) included: (1) specific formulation of the recommendation and (2) content of associated tables. Consensus was achieved for all recommendations.

Systematic literature review

The evidence base for this guideline followed the methodology by used by the Scottish Intercollegiate Guideline Network (SIGN; URL: http://www.sign.ac.uk) and Grading of Recommendations, Assessment, Development and Evaluation (GRADE; Guyatt et al. 2011). Literature from 1975 to 2010 was used to for the first review, re-evaluation, and revision of the guidelines (Kölker et al. 2011). Literature from 2011 to 2015 was used in a systematic review using MEdlINE, Embase, the Cochrane Library, Medlink, and Orphanet. Internet searches were also performed on various websites, including international and national societies for inborn errors of metabolism and support groups. Each working group selected and evaluated the literature before conclusions were considered as evidence (Supplementary Tables 1 and 2).

Grading of recommendations

Methodologies of SIGN and GRADE consider:

1. Level of evidence
2. Clinical relevance and experience
3. Balance of benefits and harms
4. General preferences and perspectives of affected individuals, resulting in recommendations likely to be implemented and acceptable

Accordingly, the GDG first graded levels of evidence as high, moderate, low, or very low, then subsequently graded recommendations by:

1. Consistency of evidence
2. Clinical relevance of endpoints
3. Clinical experience
4. Balancing benefits and harms
5. Preferences of affected individuals
6. Ethical, legal, and economic considerations
7. General practicability

For maximum transparency, information on level of evidence, consistency of evidence, and clinical relevance that have been taken into account when arriving at a conclusion are provided for each recommendation. For details, see evidence table of systematic literature review (Supplementary Table 2).

Levels of recommendations (according to SIGN and GRADE)

Strong recommendation for/against Undesirable consequences *clearly* outweigh/do not outweigh desirable consequences:

1. Evidence is of high quality
2. High degree of certainty that effects will be achieved in practice
3. Only few side effects of therapy
4. A a high degree of acceptance among affected individuals

In some cases, strong recommendations were made based on only moderate or low levels of evidence but with high clinical relevance or benefit for affected individuals.

Conditional recommendation for/against Undesirable consequences *probably* outweigh/*do not* outweigh desirable consequences:

1. Weaknesses in the evidence base
2. Degree of doubt about the size of the effect that can be expected in practice
3. Need to balance desirable and undesirable effects of therapy
4. Varying degrees of acceptance among affected individuals

Recommendation for research or conditional recommendation for use restricted to trials Balance between desirable and undesirable consequences is closely balanced or uncertain.

Recommendations and statements

Recommendations support specific interventions based on a certain level of evidence and/or clinical factors, whereas statements provide short pieces of advice that may not have an evidence base but are seen as essential to good clinical practice.

Disclaimer

The proposed recommendations are not intended to serve as a standard of management and care for affected individuals. Standards of care are formulated on the basis of all clinical data available and are influenced by scientific progress. Adherence to these recommendations will not ensure correct diagnosis and beneficial outcome in all affected individuals. Final clinical assessments must be made by experienced healthcare professional(s) and should include discussions of diagnostic and therapeutic options with affected individuals and their families. However, the recommendations will provide a rational basis for decisions in clinical management of GA-I.

Alterations since the first revision in 2011

To the best of our knowledge, none of the recommendations in the previously published guideline (Kölker et al. 2011) has been proven invalid. However, changes of recommendations grades have been made based on new evidence, integration of clinical relevance and experience, the perspective of affected individuals, and other aspects of the SIGN and GRADE methodology. Two recommendations (nos. 12 and 17),and five statements have been added to the guideline. Previous recommendations nos. 11, 12, 13, and 16 have been merged into one summarizing recommendation (no. 10), and previous recommendations nos. 2 and 3 have been summarized in Recommendation no. 2, resulting in a reduced total number of recommendations from 21 to 17.

Diagnostic procedures

Differential diagnoses

Diagnosis of GA-I is confirmed by significantly reduced enzyme activity and/or detection of disease-causing mutations on both *GCDH* alleles. All other signs, symptoms, and laboratory abnormalities found in affected individuals are suggestive but not confirming. These nonspecific signs include macrocephaly, encephalopathy, basal ganglia injury, white matter disease, movement disorders such as dystonia and chorea, subdural and retinal hemorrhages, and elevated concentrations of GA, 3-OH-GA, and C5DC in body fluids.

Phenotypic differential diagnoses of GA-I include:

1. Benign familiar macrocephaly, communicating hydrocephalus,
2. Metabolic diseases associated with macrocephaly (e.g., Canavan disease),
3. Metabolic encephalopathies leading to basal ganglia injury (e.g., Leigh syndrome in mitochondrial disorders),
4. Metabolic stroke in classic organic acidurias, urea cycle defects, and mitochondrial disorders [e.g., myopathy, encephalopathy, lactic acidosis, strokelike episodes (MELAS) syndrome,
5. nonmetabolic causes of striatal injury (e.g., infections caused by *Mycoplasma pneumoniae*),
6. Nonmetabolic encephalopathies (encephalitis, meningitis, intoxication),
7. Infantile cerebral palsy or child abuse.

Biochemical differential diagnoses of elevated concentrations of GA and 3-OH-GA are summarized in Supplemental Table 4.h

	Recommendation no. 1
Strong recommendation for	When GA-I is suspected, diagnostic workup, development of treatment plans, appropriate information and training of affected individuals and their families should take place in a specialized metabolic center. Affected individuals should be transferred to such centers without delay.
Level of evidence	One study (SIGN level 2++) has demonstrated positive effect of supervision by a metabolic center (Heringer et al. 2010).
Clinical relevance	High.

Newborn screening

GA-I is a reasonable candidate for NBS (Thomason et al. 1998; Watson et al. 2006) and has been included in the disease panels of MS/MS-based NBS in many countries worldwide (Loeber et al. 2012).

Major aims Neonatal diagnosis and start of treatment increase probability for an asymptomatic disease course (Bijarnia et al. 2008; Boneh et al. 2008; Couce et al. 2013; Heringer et al. 2010; Hoffmann et al. 1996; Kölker et al. 2006, 2007a; Lee et al. 2013; Naughten et al. 2004; Strauss et al. 2003, 2007, 2011; Viau et al. 2012). The aim of NBS is to reduce the risk of irreversible neurologic disease following striatal damage.

Definitions Population-wide newborn mass screening for GA-I is performed by MS/MS analysis of acylcarnitines in DBS, whereas high-risk screening is performed in neonates with a known increased a priori risk.

MS/MS The diagnostic metabolite in GA-I is C5DC in DBS. Some laboratories also use ratios to other measured acylcarnitines as secondary parameters (Lindner et al. 2006). Introduction of multiple reaction monitoring (MRM) to MS/MS analysis has increased sensitivity and reduced the rate of false-positive results (Screening reports of German Society for Newborn Screening 2015).

Cutoff levels A C5DC value above the cutoff is considered a positive screening result and requires follow-up. Each laboratory has to define a cutoff level for C5DC based on its own methodology and patient population. Controlled studies defining pathological values (of acylcarnitines and/or GA and 3-OH-GA) do not exist.

Diagnostic pitfalls NBS does not reliably identify all patients, especially low excreters with a normal or only slightly increased C5DC concentration in DBS (Gallagher et al. 2005; Heringer et al. 2010; Smith et al. 2001; Treacy et al. 2003; Wilcken et al. 2003). Sensitivity for C5DC screening was 95 % in one study (Heringer et al. 2010). Thus, a negative NBS result does not unambiguously exclude the diagnosis of GA-I. New analytical methods have been developed to improve detection of low excreters (Estrella et al. 2014; Moore et al. 2012). Differential diagnosis of increased C5DC concentration comprises multiple acyl-CoA dehydrogenase deficiency, renal insufficiency (Hennermann et al. 2009), and maternal GA-I (see below).

Maternal GA-I In several cases, diagnosis of maternal GA-I followed diagnostic workup of an initially decreased concentration of free carnitine or increased C5DC in NBS of the child. Biochemical parameters in these children normalized during the following weeks (Crombez et al. 2008; Garcia et al. 2008; Vilarinho et al. 2010).

> **Statement 1:** Maternal GA-I should be included in the differential diagnoses if NBS shows (1) decreased free carnitine or (2) increased C5DC but diagnostic confirmation in the child is negative or no other adequate explanation for initial abnormal screening results can be found.

For diagnostic workup in subpopulations from genetic isolates with a high carrier frequency and incidence of GA-I, alternative diagnostic procedures have been recommended (Kölker et al. 2011), i.e., direct mutation detection in addition to MS/MS NBS in at-risk babies from most known populations with low-excreter GA-I (Greenberg et al. 2002).

Confirmation of a positive screening result

Pathological NBS results should be repeated on the same DBS (and if possible by the same laboratory) and confirmed by one or more alternative techniques, including quantitative analysis of GA and 3-OH-GA in urine and/or blood with GC/MS (Al-Dirbashi et al. 2005; Baric et al. 1999; Shigematsu et al. 2005), mutation analysis of the *GCDH* gene (Goodman et al. 1998; Zschocke et al. 2000), and/or GCDH enzyme analysis in leukocytes or fibroblasts (Baric et al. 1999; Christensen 1983; Goodman et al. 1998).

Normal urine or blood 3-OH-GA level is not suggestive for GA-I but does not definitely exclude it, since some low excreters intermittently present with normal concentrations. In contrast, elevated levels of 3-OH-GA are highly suggestive for GA-I. Pitfalls for abnormal results of organic acid analysis

in urine should always be considered (Supplementary Table 4).

Specific therapy should be immediately initiated if suggestive biochemical results are present, i.e., before molecular genetic and/or enzymatic analysis confirms the diagnosis (Fig. 1). Detection of an (assured or likely) disease-causing genotype confirms the diagnosis. Sensitivity of genetic analysis is 98–99 % (Zschocke et al. 2000). There is evidence for a correlation of the genotype with biochemical parameters and residual enzyme activity but not with clinical phenotype (Christensen et al. 2004; Goodman et al. 1998; Kölker et al. 2006). Therefore, all diagnosed individuals should receive the same

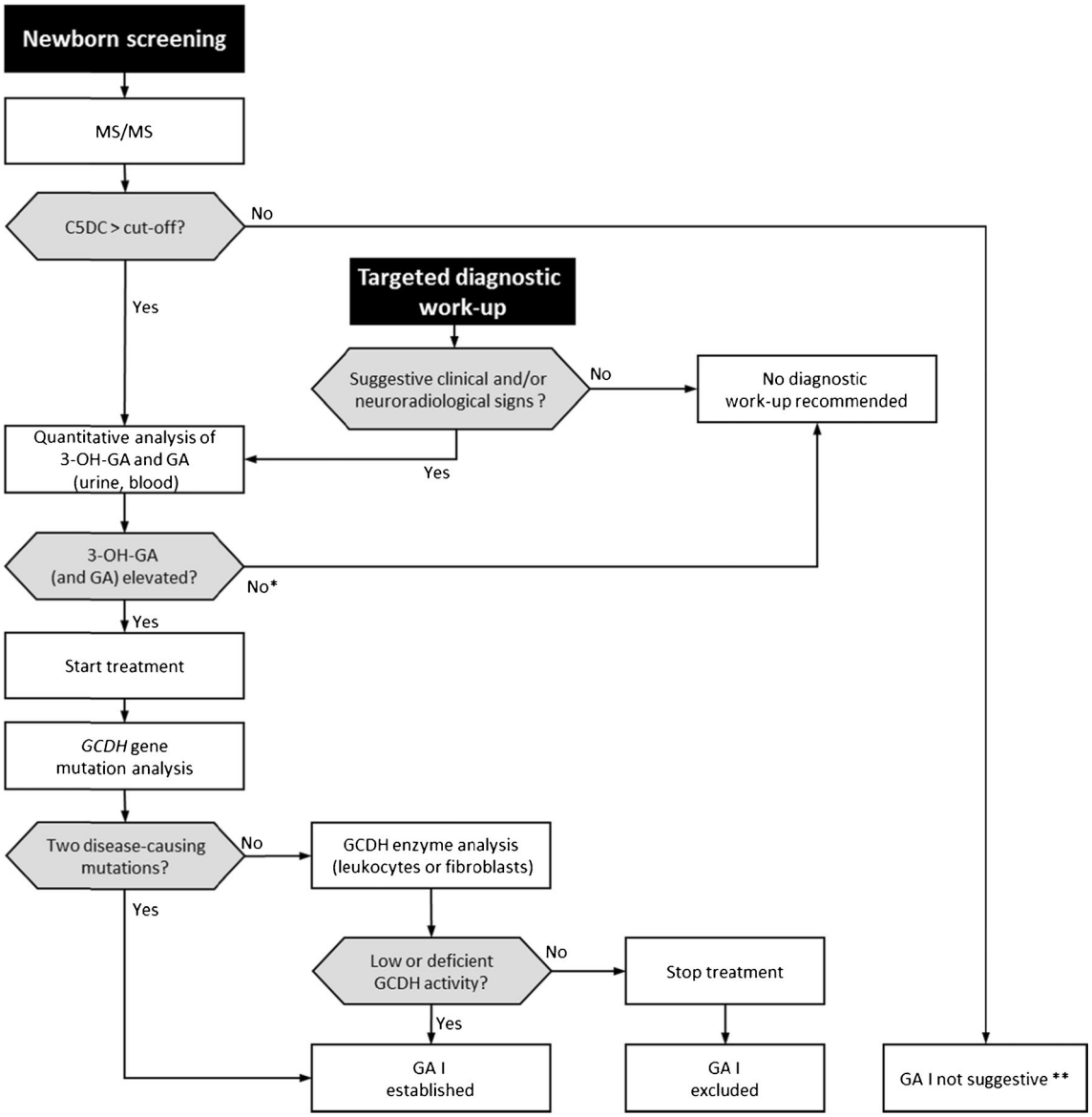

Fig. 1 Diagnostic algorithm for glutaric aciduria type I (GA-I). Newborn screening is performed using tandem mass spectroscopy (MS/MS) analyzing glutarylcarnitine (C5DC) concentration in dried blood spots (DBS). Diagnostic workup includes quantitative analysis of GA and 3-hydroxyglutaric acid (3-OH-GA) in urine and/or blood, molecular genetic analysis of *GCDH* gene, and glutaryl-CoA dehydrogenase (GCDH) enzyme analysis. Targeted diagnostic workup due to suggestive clinical, biochemical, and/or neuroradiological signs starts with quantitative analysis of GA and 3-OH-GA in urine and/or blood and is performed in analogy to the described diagnostic workup procedure. *Low-excreters may show (intermittently) normal concentrations of 3-OH-GA (and GA) in urine or blood. If highly suspicious signs and symptoms for GA-I are present, further diagnostic studies should be considered, but the decision should be made based on the individual circumstance. **If individuals in this group show suggestive clinical symptoms, diagnostic workup according to targeted diagnostic workup is recommended. Comment on mutation and enzyme analysis: Since *GCDH* gene analysis is more broadly available than GCDH enzyme analysis, and since the identification of two disease-causing mutations not only confirms the diagnosis but also enables accurate genetic counselling and prenatal diagnosis, we recommend starting with *GCDH* gene analysis. However, depending on local availability and experience, GCDH enzyme analysis could be performed first

form of treatment. Figure 1 summarizes the diagnostic algorithm for GA-I.

A special *GCDH* variant with dominant negative effect and abnormal NBS result has been reported in one family. Residual enzyme activity was 10–20 % (significantly lower than other heterozygous individuals and in the range of symptomatic GA-I subjects), and no clinical or neuroradiologic abnormalities were observed (Bross et al. 2012). At present, it is unclear whether treatment is indicated in such individuals. In general, however, heterozygous carrier status is not considered as being pathologic, since heterozygous individuals remain asymptomatic without treatment.

If only one (or no) known disease-causing mutation can be detected but other clinical biochemical and/or neuroradiologic features suggestive for GA-I are found, GCDH activity should be determined in leukocytes or fibroblasts. Significantly reduced activity will confirm the diagnosis, while normal activity (or values in the range of heterozygous carriers) will exclude it. In symptomatic individuals, residual enzyme activities of up to 30 % have been reported (Christensen et al. 2004; Kölker et al. 2006). GCDH enzyme studies may also be determined prior to genetic studies according to local availability.

Targeted diagnostic workup due to suggestive clinical signs

Targeted diagnostic workup has become less important since the initiation of NBS programs but is still relevant for individuals born before this era, in countries without screening programs, and for low excreters who may have been missed by NBS. If a patient shows suggestive clinical signs or symptoms and/or neuroradiologic findings (Supplementary Table 3), or if specific biochemical abnormalities have been detected, a targeted diagnostic workup should always be performed, even if NBS was normal. In addition, GA-I should be specifically excluded by biochemical and/or genetic analyzes in siblings of individuals with GA-I. Suggestive clinical signs include acute neurologic symptoms occuring during febrile illness or other catabolic states, such as acute or chronic onset of movement disorder (dystonia, chorea, etc.), epilepsy, truncal muscular hypotonia, or dysarthria (Badve et al. 2015; Fraidakis et al. 2015; Gupta et al. 2015; Kamate et al. 2012; Kölker et al. 2015a, b; Ma et al. 2013a, b; Wang et al. 2014; Zaki et al. 2014). Individuals with a late-onset form might present with nonspecific neurologic signs such as polyneuropathy, incontinence, headache, early-onset dementia, or tremor (Herskovitz et al. 2013; Külkens et al. 2005; Pierson et al. 2015). Neuroradiologic abnormalities occur frequently (Brismar and Ozand 1995; Doraiswamy et al. 2015; Garbade et al. 2014; Harting et al. 2009; Mohammad et al. 2015; Strauss et al. 2007; Singh et al. 2011; Vester et al. 2015) and are summarized in Supplementary Table 3.

Methods Targeted diagnostic workup uses the same methods as confirmatory diagnostic workup of abnormal NBS results, i.e., quantitative analysis of GA and 3-OH-GA in urine and/or blood by GC/MS, molecular genetic analysis of *GCDH* gene and GCDH enzyme analysis in leukocytes or fibroblasts (Fig. 1). In individuals with secondary carnitine depletion and low excreters, sensitivity of MS/MS analysis of acylcarnitines in DBS or plasma is reduced. Analysis of urinary C5DC is an alternative method but with low availability (Tortorelli et al. 2005) and lower sensitivity than quantitative analysis of 3-OH-GA in urine by GC/MS (Al-Dirbashi et al. 2010). Use of in vivo loading tests using lysine or prolonged fasting tests is potentially harmful and obsolete. Additional use of in vitro loading tests does not increase diagnostic sensitivity (Schulze-Bergkamen et al. 2005). Figure 1 summarizes the diagnostic algorithm for GA-I.

	Recommendation no. 2
Strong recommendation for	Positive NBS result and suggestive clinical, biochemical, and/or neuroradiologic signs should be confirmed by diagnostic workup, including quantitative analysis of GA and 3-OH-GA in urine and/or blood, mutation analysis of *GCDH* gene, and/or GCDH enzyme analysis in leukocytes or fibroblasts (Fig. 1).
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is high.
Clinical relevance	High.

NBS newborn screening, *GA-I* glutaric aciduria type I, *3-OH-GA* 3-hydroxyglutaric acid, *GCDH* glutaryl-CoA dehydrogenase, *SIGN* Scottish Intercollegiate Guidelines Network

Diagnosis may also be made by genetic testing without previous biochemical analysis (Marti-Masso et al. 2012). This procedure may become more important in the future due to growing availability and use of genome-wide, massively parallel, DNA sequencing techniques.

Subdural hemorrhage (SDH) and arachnoid cysts

Although SDH might appear at any age in GA-I, it peaks in late infancy when the extent of macrocephaly is greatest (Brismar und Ozand 1995; Carman et al. 2012; Hartley et al. 2000; Köhler und Hoffmann 1998; Twomey et al. 2003; Vester et al. 2015; Woelfle et al. 1996). Exact frequency of SDH is unknown, since affected individuals may remain asymptomatic. SDH in GA-I may be mistaken as abusive head trauma (Hartley et al. 2000; Morris et al. 1999; Vester et al. 2015; 2016) and thus might be a diagnostic pitfall.

Bilateral temporal fluid collections including the anterior temporal CSF spaces and the Sylvian fissure have been described and are highly suggestive for GA-I (Hald et al. 1991; Jamjoom et al. 1995; Martinez-Lage et al. 1994; Lütcherath

et al. 2000). While typically bilateral, they may be asymmetric and even space occupying, with hydrocephalus (Jamjoom et al. 1995). Bitemporal arachnoid cysts have only been verified in one of two patients on craniotomy (Lütcherath et al. 2000); however, differentiation from frontotemporal hypoplasia may be challenging. In a recently published review, diagnosis in 16/20 individuals with GA-I was made after targeted diagnostic workup due to SDH. In almost every case, additional characteristic neuroradiologic abnormalities for GA-I were present (Vester et al. 2015).

	Recommendation no. 3
Strong recommendation for	In children with SDH (including suspicion of shaken baby syndrome) and/or bitemporal fluid collections suggesting frontotemporal hypoplasia and/or arachnoid cysts, a diagnostic workup using the algorithm for targeted diagnostic workup (Fig. 1) is strongly recommended.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

SDH subdural hemorrhage, *SIGN* Scottish Intercollegiate Guidelines Network

Statement 2: SDH is usually found in combination with other neuroradiologic abnormalities characteristic for GA-I (i.e., frontotemporal hypoplasia, enlarged CSF spaces etc., Supplementary Table 3). Isolated SDH without these characteristic abnormalities per se is not suggestive for GA-I and should not result in targeted diagnostic workup.

Metabolic maintenance treatment

Start of treatment

When GA-I is suspected during diagnostic workup (Fig. 1), i.e., due to elevated concentration of 3-OH-GA in urine, metabolic treatment should be started immediately. Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require the expertise of specialized metabolic centers, including specialists in inherited metabolic diseases, genetic counselors, dieticians, nurses, physiotherapists, occupational therapists, speech therapists, psychologists, and social workers. Regular follow-up by metabolic expert centers significantly increases the probability of an asymptomatic disease course (Heringer et al. 2010).

	Recommendation no. 4
Strong recommendation for	Metabolic treatment and regular follow-up monitoring should be implemented by an interdisciplinary team in a specialized metabolic center.
Level of evidence	High to moderate (SIGN level 2++ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

SIGN Scottish Intercollegiate Guidelines Network

Effectiveness of treatment

When diagnosis is made after manifestation of neurologic disease, outcome is poor, and therapeutic impact is limited (Busquets et al. 2000; Bjugstad et al. 2000; Hoffmann et al. 1996; Kamate et al. 2012; Kyllerman et al. 2004; Kölker et al. 2006; Wang et al. 2014), though some affected individuals may benefit by prevention of progressive neurologic deterioration (Badve et al. 2015; Bjugstad et al. 2000; Hoffmann et al. 1996; Kölker et al. 2006; Strauss et al. 2003; Fraidakis et al. 2015).

In contrast, 80–90 % of individuals with GA-I remain asymptomatic if treatment is started in the newborn period before symptom onset (Afroze and Yunus 2014; Bijarnia et al. 2008; Boneh et al. 2008; Boy et al. 2013; Couce et al. 2013; Gokmen-Ozel et al. 2012; Heringer et al. 2010; Kölker et al. 2006, 2007a, 2012; Lee et al. 2013; Naughten et al. 2004; Radha Rama Devi et al. 2016; Strauss et al. 2003, 2007, 2011; Viau et al. 2012). Combined metabolic therapy consists of low-lysine diet, carnitine supplementation, and emergency treatment during episodes, inducing catabolism, and allows for normal development and growth (Boy et al. 2013). Individuals adhering to treatment recommendations rarely develop dystonia (5 %), while nonadherence to maintenance treatment increases the rate to 44 % and nonadherence to emergency treatment to 100 % (Heringer et al. 2010).

Dietary treatment

International recommendations and individualization of treatment Dietary recommendations considering age-dependent needs of a growing child have been developed by international organizations such as the World Health Organization (WHO) or German, Austrian and Swiss Nutrition Societies (D-A-CH). Recommendations may vary significantly due to the use of different protein requirements and the use of average versus safe levels. Recommendations are usually set to the safe level [= mean + 2 standard deviations (SD) of daily required intake]. GDG members most

commonly use the revised safe levels (Dewey et al. 1996) and D-A-CH recommendations (2000) for calculating individualized dietary protocols. These recommendations have been used in several clinical trials and have resulted in a positive outcome (Boy et al. 2013; Heringer et al. 2010; Kölker et al. 2007a, 2012). Nutrient intake and energy recommendations by D-A-CH were revised in 2015 (D-A-CH 2015) and are similar to D-A-CH (2000) and joint WHO/Food and Agriculture Organization (FAO)/United Nations University (UNU) expert consultation (World Health Organization 2007).

Principles of low-lysine diet until age 6 years Dietary treatment for GA-I aims to reduce the intake of lysine, quantitatively the most relevant amino acid precursor of neurotoxic GA and 3-OH-GA, while maintaining sufficient intake of essential nutrients and energy substrates (Table 2 and Supplementary Table 5). In the mouse model for GA-I, cerebral concentrations of GA and 3-OH-GA positively correlated with the amount of dietary lysine intake (Sauer et al. 2011; Zinnanti et al. 2007). Since in vivo measurement of metabolites requires invasive methods, analogous data for individuals with GA-I are scarce, and knowledge is based on a post mortem study (Kölker et al. 2003).

Limitation of protein intake concomitantly reduces lysine intake. However, the lysine content in natural foods varies considerably, e.g., 2–4 % (lysine/protein) in cereals and 9 % (lysine/protein) in fish (Supplementary Table 5). Therefore, direct calculation of lysine intake instead of total natural protein intake is more precise and reduces long-term day-to-day variability of lysine intake (Müller and Kölker 2004; Yannicelli et al. 1994). This approach has been used in several clinical trials. In addition to decreased lysine intake, individuals with GA-I also received lysine-free, tryptophan-reduced, amino acid mixtures (AAM) aiming to provide adequate supply of essential amino acids and–with some product-specific variation–also minerals, trace elements, and vitamins. This nutritional therapy (low-lysine diet and AAM supplementation) combined with carnitine supplementation and intensified emergency treatment has been associated with the most favorable neurologic outcome and normal growth in several studies (Boy et al. 2013; Heringer et al. 2010; Kölker et al. 2006, 2007a, 2012; Lee et al. 2013; Strauss et al. 2011; Viau et al. 2012). In contrast, less pronounced clinical effect was demonstrated in cohorts on a low-protein diet using calculation of protein intake (instead of lysine) and omitting AAM (Boneh et al. 2008; Greenberg et al. 2002; Strauss et al. 2007).

Tryptophan Tryptophan content in natural protein is only 0.6–2 %; its quantification in plasma is technically challenging, and depletion may cause severe neurologic deficits (Hoffmann et al. 1991). Thus, AAM used for dietary treatment should be tryptophan reduced but not tryptophan free.

Arginine It has been proposed that the reduction of lysine transport across the blood–brain barrier caused by arginine, which competes with lysine for uptake via the CAT1 transporter, can be exploited for treatment, an approach that has

Table 2 Metabolic maintenance treatment

Treatment		Age				
		0–6 months	7–12 months	1–3 years	4–6 years	>6 years
1. Low-lysine diet						
Lysine (from natural protein)[a]	mg/kg per day	100	90	80–60	60–50	Controlled protein intake using natural protein with a low-lysine content and avoiding lysine-rich food; e.g., according to national recommendations such as Optimix[d]
Amino acid mixtures (protein)[b]	g/kg per day	1.3–0.8	1.0–0.8	0.8	0.8	
Energy	kcal/kg per day	100–80	80	94–81	86–63	
2. Micronutrients[c]	%	≥100	≥100	≥100	≥100	≥100
3. Carnitine	mg/kg per day	100	100	100	100–50	50–30

If normal growth and development are not achieved these recommendations should be modified according to individual needs

[a] Lysine/protein ratios vary considerably in natural food, and thus, natural protein intake in children on a low-lysine diet is dependent on the natural protein source. Natural protein intake is relatively high if patients predominantly use natural protein with a low-lysine content. For this reason, numerical data on natural protein are not provided

[b] Lysine-free, tryptophan-reduced amino acid mixtures should be supplemented with minerals and micronutrients as required to maintain normal levels. Adequate intake of essential amino acids is provided from natural protein and lysine-free, tryptophan-reduced, amino acid supplements. The amount of amino acid supplements is adjusted to reach at least the safe levels (Dewey et al. 1996)

[c] According to international dietary recommendations (D-A-CH 2015)

[d] Optimix®, National Nutritional Recommendations for Children and Adolescents, by Research Institute for Child Nutrition Dortmund, Germany; URL: http://www.fke-do.de/index.php

been termed complementary diet therapy (Kölker et al. 2012; Strauss et al. 2011). Arginine is a semiessential amino acid that can be synthesized via the urea cycle and for which minimal requirements have not been defined. Only 40 % of dietary arginine reaches circulation after intestinal digestion and metabolism (Castillo et al. 1993). The arginine content of natural protein varies considerably, as does the amount of arginine in commercially available AAMs used during the first year of life. As a result, the daily arginine intake in infants with GA-I can vary significantly depending on the amount and type of natural protein and lysine-free, tryptophan-reduced AAM in their diet. There is less variability in the arginine content of AAMs used in older children and adults, but nonetheless, daily intake of arginine can vary depending on the type and amount of natural protein included in the diet. Despite this potential variability, clinical outcomes including motor development and risk of movement disorder are similar, regardless of the arginine content of the AAM being used (Kölker et al. 2012). Studies in a mouse model showed that arginine supplementation can reduce cerebral concentrations of neurotoxic metabolites (GA, 3-OH-GA) but only when given at supraphysiologic doses (Sauer et al. 2011). In the same study, it was found that a low-lysine diet was much more effective in reducing cerebral levels of neurotoxic metabolites. There is insufficient evidence to support high-dose arginine supplementation orally in addition to, or as a substitute for, the use of a lysine-free, tryptophan-reduced, arginine-containing AAM.

During acute illness, decreased concentrations of plasma arginine levels have been reported in some individuals with GA-I (Strauss et al. 2011). However, clinical relevance of this observation is unknown, and low-arginine plasma levels are a common phenomenon in acute illness independent from GA-I due to enhanced use of arginine via the arginase and nitric oxide pathways (Luiking et al. 2005). There is no evidence for arginine therapy IV during acute illness in GA-I.

> **Statement no. 3:** There is no evidence for a clinical benefit of high-dose arginine supplementation orally for maintenance treatment or for the use of arginine IV for emergency treatment. For this reason, arginine intake should only be provided by lysine-free, tryptophan-reduced, arginine-containing AAM and natural protein within a balanced low-lysine diet.

Dietary treatment after age 6 years Long-term outcome in GA-I is largely unknown. Besides acute encephalopathic crises, there is increasing evidence for the occurrence of late-onset and insidious-onset disease variants (Bähr et al. 2002; Busquets et al. 2000; Fernández-Álvarez et al. 2003; Harting et al. 2009; Hoffmann et al. 1996; Külkens et al. 2005; Pierson et al. 2015; Strauss et al. 2007). Acute and insidious disease onset manifest during the first 6 years of life, whereas individuals with late onset often present during adolescence or adulthood. There is also evidence for variable progressive extrastriatal MRI changes after age 6 years (Harting et al. 2009), but clinical relevance is unclear. Effectiveness of dietary treatment after 6 years has not been systematically studied. However, as the clinical course is unknown, controlled protein intake using natural protein with a low lysine content and avoiding lysine-rich food is advisable after age 6 years (e.g., according to national recommendations such as Optimix®, formulated by the Research Institute of Child Nutrition, Dortmund, Germany). To prevent growth disturbance or malnutrition, change from low-lysine diet before to protein-controlled diet after age 6 years and the following period should be accompanied by regular dietary advice.

Recommendation 5	
Strong recommendation for	Low-lysine diet with additional administration of lysine-free, tryptophan-reduced AAMs containing essential amino acids is strongly recommended for dietary treatment up to age 6 years.
Level of evidence	High to moderate (SIGN level 2++ to 4). Consistency of evidence is high.
Clinical relevance	High.

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Recommendation no. 6	
Recommendation for	After age 6 years, dietary treatment should follow an age-adapted, protein-controlled protocol based on safe levels for protein intake. Dietary changes should be accompanied by regular dietary advice.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is high.
Clinical relevance	High.

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Infant feeding Breast milk is physiological and beneficial for infants (Dewey et al. 1995), but except for phenylketonuria (PKU), evidence for successful breastfeeding of babies with inherited metabolic diseases is limited to few publications (Huner et al. 2005; MacDonald et al. 2006). Breastfeeding in infants with GA-I should be encouraged. The GDG is most experienced in breastfeeding on demand after giving certain amounts of lysine-free and tryptophan-reduced AAM, thus limiting lysine intake in analogy to PKU (Francis and Smith 1981). This procedure is associated with beneficial clinical outcome (Boy et al. 2013; Heringer et al. 2010;

Kölker et al. 2007a, 2012). Clinical experience with administration of infant formula after breastfeeding is scarce (van Rijn et al. 2003). Since the amount of lysine in breast milk is known (86 mg/100 ml; Souci et al. 2008), daily lysine intake can be calculated when breast milk is the only natural protein source and breast milk intake is calculated and stable. As the lysine content of infant formula is also known, bottle feeding can be used to calculate lysine intake.

Children with feeding problems Children with feeding problems need skilled supervision of a metabolic dietitian. Such children may require tube feeding, pharmacotherapy, or surgery (i.e., fundoplication, gastrostomy, jejunostomy) to sustain adequate energy supply.

Individuals with dystonic movement disorder Children with severe dystonia, or *status dystonicus*, may have increased energy demand despite treatment with antidystonic medication and immobility (personal communication, B. Assmann, Heidelberg). Intensive dietary supervision is necessary in dystonic individuals to adapt energy intake and avoid catabolism and are also at increased risk of aspiration pneumonia and malnutrition due to orofacial dyskinesia (Boy et al. 2013; Kölker et al. 2007a; Müller and Kölker 2004; Yannicelli et al. 1994).

Education Effectiveness of a low-lysine diet (Heringer et al. 2010 and recommendation no. 5) critically depends upon adequate provision of information and education to parents, affected individuals, and caregivers. It is essential that they receive continued support and education from the interdisciplinary metabolic team.

Pharmacotherapy

Carnitine supplementation Secondary plasma carnitine depletion frequently occurs in untreated individuals with GA-I (Lipkin et al. 1988; Seccombe et al. 1986; Wang et al. 2014), but concomitant intracellular carnitine concentrations are unknown. Conjugation of carnitine with GA results in formation of nontoxic glutarylcarnitine and is proposed to reduce the intracellular CoA pool via increasing accumulation of glutaryl-CoA (Seccombe et al. 1986). This results in secondary carnitine depletion, which can be compensated for by carnitine supplementation orally, as demonstrated in a mouse model (Sauer et al. 2011). L-carnitine supplementation is considered to contribute to reduced risk for striatal injury in individuals diagnosed early (Couce et al. 2013; Heringer et al. 2010; Kölker et al. 2007a; Lee et al. 2013; Strauss et al. 2003, 2011; Viau et al. 2012) and reduces mortality rates in symptomatic individuals with GA-I (Kölker et al. 2006). Although no randomized controlled studies demonstrate a specific positive effect of carnitine on clinical outcome (Nasser et al. 2009; Walter 2003), lifelong carnitine supplementation is generally recommended (Bjugstad et al. 2000; Hoffmann et al. 1996; Kölker et al. 2006; Strauss et al. 2003). An initial oral dosage of 100 mg L-carnitine/kg per day divided into three doses is commonly used (Kölker et al. 2007a; Strauss et al. 2003) and then individually adjusted to maintain plasma free L-carnitine concentration within the normal range. Dosage reduction may be necessary due to adverse effects, such as diarrhea and a fishy odor.

An experimental study demonstrated increased production of trimethylamine-N-oxide (TMAO), an atherogenic metabolite of carnitine formed by intestinal microbiotic metabolism, after carnitine intake from red meat (Koeth et al. 2013). Whether long-term carnitine supplementation is associated with atherosclerosis in GA-I is unknown. At present, the benefits of carnitine supplementation are believed to outweigh the potential risks.

	Recommendation no. 7
Recommendation for	L-carnitine should be supplemented lifelong aiming to maintain a normal plasma concentration of free L-carnitine.
Level of evidence	High to moderate (SIGN level 2++ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

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Riboflavin Although certain affected individuals may show biochemical improvement (decreased GA and 3-OH-GA) following riboflavin supplementation (Brandt et al. 1979; Chalmers et al. 2006; Lipkin et al. 1988), there is no evidence that riboflavin improves the clinical outcome (Kölker et al. 2006). There is no standardized protocol for evaluating riboflavin responsiveness, and it cannot be predicted by mutation analysis. Riboflavin also causes adverse gastrointestinal symptoms such as nausea and abdominal pain.

Neuroprotective agents There is no evidence that use of other drugs, such as phenobarbitone, *N*-acetylcysteine, creatine monohydrate, topiramate, glutamate receptor antagonists, and antioxidants are beneficial in GA-I (Greenberg et al. 2002; Kyllerman et al. 1994, 2004; Strauss et al. 2003).

Table 2 summarizes recommended best practice for metabolic maintenance treatment.

Emergency treatment

Maintenance treatment alone is not sufficient for avoiding encephalopathic crises, so it is important to use intensified emergency treatment protocol if affected individuals are at risk for catabolism due to febrile illness, febrile reactions to vaccination, or perioperative/peri-interventional fasting periods (Heringer et al. 2010; Monavari and Naughten 2000; Strauss et al. 2007). Inadequate or delayed start of emergency treatment results in a high risk of striatal injury and dystonia (Heringer et al. 2010). Emergency treatment should be initiated without delay, with low clinical suspicion, and intensified stepwise (Couce et al. 2013; Heringer et al. 2010; Marigliano et al. 2013; Mushimoto et al. 2011; Lee et al. 2013; Pusti et al. 2014; Strauss et al. 2007, 2011; Viau et al. 2012).

Principles

Emergency treatment in GA-I follows the elementary treatment principles for intoxication type metabolic diseases (Dixon and Leonard 1992; Prietsch et al. 2002):

1. prevent or reverse a catabolic state by administering a high-energy intake (plus insulin in case of hyperglycemia and/or lipids if required);
2. reduce production of neurotoxic GA and 3-OH-GA by transient decrease or omitting natural protein for 24 (−48) h;
3. support physiological detoxification mechanisms and prevent secondary carnitine depletion by carnitine supplementation, and
4. balance electrolytes and pH status via IV fluids.

Emergency treatment

Preventive care Delaying emergency treatment is associated with significant risk for neurologic disease (Heringer et al. 2010). To avoid this, preventive strategies should be followed (Table 3).

Start of emergency treatment Acute encephalopathic crises may occur during any febrile illness, febrile reaction due to vaccinations, or surgery during the vulnerable period (age 0–6 years). Alarming symptoms include conditions that accelerate catabolism, such as repeated vomiting and diarrhea (with or without fever), and manifestation of severe neurologic symptoms (i.e., muscular hypotonia, irritability, rigor, dystonia, reduced consciousness). After age 6 years, the risk for developing an acute crisis is considerably reduced (Bjugstad et al. 2000; Hoffmann et al. 1996; Kölker et al. 2006; Strauss et al. 2003). However, the possibility of subclinical cerebral injury cannot be excluded, and the threshold to start emergency treatment should be low in this age group (Heringer et al. 2010; Strauss et al. 2007).

	Recommendation no. 8
Strong recommendation for	It is strongly recommended to start emergency treatment without delay and to perform it aggressively during febrile illness, febrile reactions to vaccinations, or perioperative management within the vulnerable period for striatal injury (up to age 6 years).
Level of evidence	High to moderate (SIGN level 2++ to 3). Consistency of evidence is high.
Clinical relevance	Very high.

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Outpatient emergency treatment

If the individual is generally clinically well despite intercurrent infectious disease or febrile reaction to vaccinations, the body temperature is <38.5 °C (101 °F). If the diet is tolerated and no alarming symptoms (i.e., alteration in level of consciousness, diarrhea, vomiting, irritability, hypotonia, dystonia) are found, an outpatient treatment period at home of up to 12 h is recommended. The child should be reassessed every 2 h regarding state of consciousness, fever, and feeding tolerance. If parents are adequately trained, maltodextrin solutions or comparable carbohydrate supplementations can be given orally or via nasogastric tube, gastrostomy, or jejunostomy to provide sufficient energy supply. If body temperature rises >38.5 °C, antipyretics such as acetaminophen, ibuprofen, or paracetamol should be administered. If outpatient emergency treatment can be performed adequately and the child does not develop alarming symptoms, maintenance treatment should be reintroduced stepwise during the next 48 (−72) h.

Table 4 summarizes recommended best practice for outpatient emergency treatment.

Inpatient emergency treatment

If alarming symptoms such as recurrent vomiting, recurrent diarrhea, reduced nutrient intake, spiking temperature, or suspicious neurologic signs evolve, individuals should immediately be transferred to the closest hospital or metabolic center to start emergency treatment.

Table 3 Strategies to optimize emergency treatment

Target topic	Proposed strategy
Education and training of parents	Parents should be informed in detail about natural history, maintenance and emergency treatment, prognosis, and the particular risk for manifestation of an acute encephalopathic crisis. Parents should be regularly tested on this knowledge.
Treatment protocols/emergency cards	Written protocols for maintenance and emergency treatment should be regularly updated and provided to all persons involved (parents, metabolic centers, local hospitals, and pediatricians). Also, an emergency card (preferably laminated) should be provided summarizing key information and principles of emergency treatment and containing contact information of the treating metabolic center.
Supplies	Adequate supplies of specialized dietetic products (maltodextrin, lysine-free, tryptophan-reduced amino acid mixtures); medication required for maintenance and emergency treatment (carnitine, antipyretics) should always be maintained at home.
Close cooperation with local hospitals and pediatricians	After new diagnosis of GA-I in a child, the closest hospital and local pediatrician should be informed and instructed. Inpatient emergency treatment should: (1) take place in the closest hospital, (2) be started without delay, and (3) be supervised by the responsible metabolic center, which should be contacted without delay. Essential information including written treatment protocols should be provided before inpatient emergency treatment might be necessary.
Holiday management	Metabolic specialists/centers closest to the holiday resort should receive information about GA-I and recent treatment before starting the vacation. Parents should be provided with contact information of the corresponding specialist.
Consultation at metabolic center for infectious diseases	Parents or local hospitals/pediatricians should immediately inform the responsible metabolic center if: (1) temperature rises >38.5 °C; (2) vomiting/diarrhoea or other symptoms of intercurrent illness develop; (3) new neurologic symptoms occur. Management of emergency treatment should always be supervised by the responsible metabolic center.
Perioperative management	If an (elective or emergency) surgical intervention is planned, the responsible metabolic center should be informed in advance to discuss perioperative management with surgeons and anesthesiologists.

Table 5 summarizes recommended best practices for inpatient emergency treatment.

Emergency treatment after age 6 years

Although encephalopathic crises have not been reported after age 6 years (Bjugstad et al. 2000; Heringer et al. 2010; Kölker et al. 2006; Strauss et al. 2003), the possibility that febrile illness or surgical procedures could cause subclinical cerebral damage in this age period cannot be excluded. Therefore, emergency treatment after age 6 years should be liberally administered. Of note, glucose intake should always be age adapted. At present, only case reports on emergency treatment in adolescents and adults have been published (Ituk et al. 2013; Jamuar et al. 2012).

	Recommendation no. 9
Recommendation for research	Emergency treatment in children after age 6 years should be considered during severe illness or perioperative management and performed similarly to that in the age group 0–6 years, with individual adaptation.
Level of evidence	Low (SIGN level 3). Consistency of evidence is low.
Clinical relevance	Moderate.

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Pregnancy and peripartum management in women with GA-I

Management of pregnancy should be supervised by the responsible interdisciplinary team. Evidence and/or sufficient clinical experience regarding efficacy or necessity of emergency treatment during the peripartum period is not available, and recommendations cannot be made. Uneventful clinical course for mother and child has been reported for women receiving emergency treatment during the peripartum period (Ituk et al. 2013), as well as women who did not receive any specific therapy (Garcia et al. 2008). However, for surgical procedures (e.g., C-sections) Recommendation no. 9 should be regarded as valid.

Neurologic complications

The major neurologic complications in GA-I are development of a dystonic movement disorder and SDH. Frequency of epilepsy is also increased (Kölker et al. 2015a).

Management of movement disorders

Striatal injury results in a complex movement disorder mostly manifesting as dystonia and/or choreiform movements

Table 4 Outpatient emergency treatment (up to age 6 years)

Recommended best practice				
A. Oral carbohydrates (maltodextrin)[a]				
Age (years)	%*	kcal/100 ml	kj/100 ml	Volume (ml) per day orally
Up to 0.5	10	40	167	min. 150 ml/kg
0.5–1	12	48	202	120 ml/kg
1–2	15	60	250	100 ml/kg
2–6	20	80	334	1200–1500 ml
B. Protein intake				
Natural protein	According to emergency dietary plan: 50 % reduction or stop for maximum of 24 h, then reintroduce and increase stepwise until the amount of maintenance treatment is reached within 48–72 h.			
AAMs	If tolerated, administered according to maintenance therapy (see also Table 2).			
C. Pharmacotherapy				
L-carnitine	Double carnitine intake: e.g., 200 mg/kg per day p.o. in infants.			
Antipyretics	If body temperature rises >38.5 °C (101 F), antipyretics, such as ibuprofen or paracetamol (each 10–15 mg/kg per single dose, 3–4 doses daily, maximum daily dose 60 mg/kg body weight) should be administered.			

AAM amino acid mixture

[a] Maltodextrin solutions (Dixon and Leonard 1992) should be administered every 2 h day and night. Concentrations may be adapted if clinically indicated. If AAM is tolerated, it may be fortified by maltodextrin. Individuals should be reassessed every 2 h regarding level of consciousness, feed tolerance, fever, and alarming symptoms

*Volume percent, i.e., 100 g maltodextrin in 1000 ml water results in a 10 % solution

superimposed on axial hypotonia (Hoffmann et al. 1996; Kyllerman et al. 1994). Dystonia might evolve from mobile to fixed and might be associated with akinetic–rigid parkinsonism or spasticity (Gitiaux et al. 2008; Heringer et al. 2010;

Table 5 Inpatient emergency treatment (up to age 6 years)

Recommended best practice		
A. Intravenous infusions		
Glucose	Age (years)	Glucose (g/kg per day IV)
	0–1	(12–) 15
	1–3	(10–) 12
	3–6	(8–) 10
Insulin	If persistent hyperglycemia >150–180 mg/dl (>8–10 mmol/L) and/or glucosuria occurs, start with 0.025–0.05 IU insulin/kg per h IV and adjust the infusion rate according to serum glucose.	
B. Protein intake		
Natural protein	Stop for maximum of 24 h, then reintroduce and increase stepwise until the amount of maintenance treatment is reached within 48–72 h.	
AAMs	If tolerated, AAMs should be administered according to maintenance therapy (see also Table 2).	
C. Pharmacotherapy		
L-carnitine	100 mg/kg per day IV according to normal daily dose.	
Antipyretics	If body temperature rises >38.5 °C (101 F), antipyretics, such as ibuprofen or paracetamol (each 10–15 mg/kg per single dose, 3–4 doses daily, maximum daily dose 60 mg/kg body weight) should be administered.	
Sodium bicarbonate	If acidosis: alkalization of urine also facilitates urinary excretion of organic acids	
D. Monitoring		
Metabolic parameters	Blood: glucose, blood gases, creatine kinase, amino acids (plasma)[a], carnitine (plasma) Urine: ketone bodies, pH	
Routine laboratory	Electrolytes, blood count, creatinine, C-reactive protein, blood culture (if indicated)	
Vital signs	Heart rate, blood pressure, temperature, diuresis; Glasgow Coma Scale if reduced consciousness; assessment for neurologic signs (hypotonia, irritability, rigor, dystonia)	

[a] During the recovery phase

Hoffmann et al. 1996; Kyllerman et al. 1994; Kölker et al. 2006; Strauss et al. 2003).

	Recommendation no. 10
Strong recommendation for	Neurologic (i.e., epilepsy, movement disorder) or neurosurgical (SDH) complications should be managed by a neuropediatrician (later neurologist) and/or neurosurgeon in close cooperation with the metabolic specialist.
Level of evidence	Moderate (SIGN level 2− to 3).
Clinical relevance	High.

SDH subdural hemorrhage, *SIGN* Scottish Intercollegiate Guidelines Network

Dystonia rating scales

Objective assessment of movement disorders includes evaluation of clinical localization, severity, and effectiveness of treatment. The Barry-Albright Dystonia Rating Scale (Barry et al. 1999; Monbaliu et al. 2010) has been used in some studies (Boy et al. 2015; Heringer et al. 2010) but may be of limited use in infants and young children, since it likely underestimates the severity of movement disorders in this age group due to severe truncal hypotonia (Heringer et al. 2010). The Burke-Fahn-Marsden Dystonia Rating Scale (Elze et al. 2016) has also been used in children but not specifically in GA-I. The Gross Motor Function Classification System (GMFCS) is widely used in different neurologic conditions in children, and although it does not specifically evaluate dystonia, it is a helpful and standardized test to analyze global motor impairment.

Drug therapy

In general, treating movement disorder associated with GA-I is challenging, with little evidence regarding the effectiveness of specific drugs (Burlina et al. 2004).

Baclofen Together with benzodiazepines, baclofen (mono- or combination therapy) orally is the mostly widely used and apparently effective drug for long-term treatment of movement disorders in GA-I (Hoffmann et al. 1996; Kyllerman et al. 1994) and should be used in dosages according to general recommendations. Baclofen administered intrathecally was successful in severely dystonic indiviuals with GA-I (Kyllerman et al. 2004). In younger children with prominent axial hypotonia, use of baclofen may be limited due to worsening of reduced muscle tone.

Benzodiazepines Diazepam and clonazepam show positive effects in >90 % of symptomatic individuals (Hoffmann et al. 1996; Kyllerman et al. 1994, 2004). Dosages should be administered according to general recommendations. In individuals with variable symptoms, the daily dosage may be adjusted within a given range. To prevent tachyphylaxis, intermittent treatment may be necessary.

Zopiclone, a cyclopyrrolone used as a hypnotic drug primarily in nonmetabolic dystonia, has shown positive effects in some affected individuals (personal communication, B. Assmann, Heidelberg) by reducing the hyperkinetic proportion of movement disorders and general muscle tone due to its sedative, hypnotic, anxiolytic, and muscle-relaxant qualities. In contrast to other benzodiazepines, its pharmacodynamic effect is mediated by the gamma-aminobutyric acid A (GABA-A) receptor (BZ1 and BZ2 subunits) and modulation of chloride channel with a low risk of developing tolerance and addiction. Treated individuals are more relaxed and awake during the day, as they are less affected by their movement disorder during night time. Cautious dose adaption and stepwise reduction is important and preferably provided on an inpatient basis. If treatment with baclofen and/or benzodiazepines is not effective or adverse effects occur, anticholinergic drugs should be considered as second-line medication.

Anticholinergic drugs Trihexyphenidyl can be effective in treating dystonia (Burlina et al. 2004), especially in adolescents and adults, but it may also be effective in children if dosage is slowly increased. However, adverse effects (i.e., temporary symptoms such as blurred vision and dry mouth or persisting symptoms such as memory loss and confusion) occur frequently, and hyperkinetic dystonia (Rice and Waugh 2009; Sanger et al. 2007) may be worsened. Ocular tonometry should regularly be performed in adults.

Botulinum toxin Botulinum toxin type A may help prevent hip dislocation and reduce limb dystonia (Burlina et al. 2004). Some individuals may develop antibodies against the toxin, and treatment cessation may be necessary. It is usually administered every 3–6 months.

Drugs without proven benefit or with adverse effects Some antiepileptic drugs without significant clinical effect have been used (Hoffmann et al. 1996; Kyllerman et al. 1994, 2004). Vigabatrin and valproate showed clinical benefit in 10–25 %: vigabatrin may induce peripheral visual field defects as a putative side effect; valproate may influence mitochondrial acetyl-CoA/CoA ratio negatively. Therefore, neither drug should be used to treat GA-I. Carbamazepine, L-DOPA, and amantadine are ineffective. Gabapentin can significantly improve dystonia due to diverse conditions (Liow et al. 2016); however, results in GA-I have not been reported.

Antiepileptic therapy

Risk for epilepsy is increased in GA-I (Kölker et al. 2015a), and seizures may be the first or sole symptom of the disease (McClelland et al. 2009). Single seizures may be observed during an acute encephalopathic crisis (Greenberg et al. 2002; Kölker et al. 2006; Kyllerman et al. 2004; Strauss et al. 2003), but infantile spasms and hypsarrhythmia have also been reported in the absence of encephalopathy (Young-Lin et al. 2013); dystonic movements may be mistaken as seizures (Cerisola et al. 2009). No study has analyzed the effectiveness of antiepileptic agents in GA-I. However, as previously mentioned, valproate and vigabatrin should be avoided. The choice of antiepileptic drug used in individuals with epilepsy should be derived from individual semiology of seizures and/or specific electroencephalogram (EEG) patterns.

Neurosurgery

Stereotactic surgery (pallidotomy) has been performed in three severely dystonic individuals with GA-I. In two, clinical outcome was poor (Strauss et al. 2003), whereas short-term improvement of dystonia was reported in another (Rakocevic et al. 2004). Data on long-term outcome after pallidotomy have not been published. Deep brain stimulation has been performed in four cases, with some positive results (Air et al. 2011; Lumsden et al. 2013).

Subdural hemorrhage and arachnoid cysts

Neurosurgery There are few reports of individuals with GA-I undergoing neurosurgical procedures to treat arachnoid cysts and/or SDH (Hald et al. 1991; Lütcherath et al. 2000; Martinez-Lage et al. 1994; Woelfle et al. 1996). Postinterventional neurologic outcome was mostly poor, and symptoms were often worsened. In addition, neurosurgical interventions in undiagnosed individuals without treatment increase the risk for acute encephalopathic crisis. See Recommendation no. 10 for management of neurosurgical complications. Perioperative metabolic management should be based on recommendations mentioned above, and therapy should be supervised by a metabolic specialist (see Recommendations nos. 4–9).

Monitoring

General aims

The aim of regular clinical monitoring is to assess the treatment effectiveness and identify any new symptoms, complications, or side effects of dietary or pharmacologic treatment. In general, monitoring should include parameters that:

1. Are reliable and predictive for clinically relevant outcome
2. Allow therapeutic decisions
3. Have acceptable reproducibility to allow use for short-term monitoring,
4. Are sufficiently affordable and
5. Are practical (Glasziou et al. 2005). For GA-I, no specific marker reliably predicts the clinical outcome. Therefore, monitoring should include all anthropometric, neurologic, biochemical, cognitive, and therapeutic parameters summarized in Table 6.

Clinical monitoring

GA-I is associated with an increased risk of severe neurologic disease, and treatment must be adapted specifically to each patient. Clinical monitoring is important to ensure adherence to treatment recommendations, which are essential to prevent significant neurologic injury and possible early death. Frequent monitoring can also help to reassure patients and their families that the recommended treatments are being effective, which helps maintain compliance. Regular clinical monitoring should include anthropometrics, developmental milestones, neurologic assessment, specific psychological tests, and dietary parameters. Although overall cognitive outcome may be normal, subtle cognitive deficits, mainly in speech development and fine-motor function, may be found (Beauchamp et al. 2009; Harting et al. 2009). Expertise from general pediatricians, metabolic specialist, and dietitians, as well as consultations from other specialities (e.g., neuropediatricians, psychologists, physiotherapists, occupational therapists, and social workers), should be included in the evaluation and monitoring of individuals with GA-I.

Table 6 summarizes recommended best practices for clinical monitoring.

	Recommendation no. 11
Strong recommendation for	Therapeutic effectiveness should be monitored by regular follow-up and intensified at any age if symptoms progress, new symptoms manifest (disease or therapy related), or nonadherence to treatment recommendations is suspected. For clinical endpoints of monitoring, see Recommendations nos. 13–17.
Level of evidence	High to moderate (SIGN level 2++ to 3).
Clinical relevance	Depending on particular endpoint.

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Table 6 Clinical monitoring

Domain	Clinical endpoints	Frequency at age			
		0–1 year	1–6 years	>6 years	>18 years
History	General history and development, intercurrent infections, outpatient or inpatient emergency treatment, dietary treatment, pharmacotherapy, vaccinations, regular pediatric preventive examinations	Every 3 months	Every 6 months	1/year	1/year
Anthropometics	Body weight, body length, head circumference	Every 3 months	Every 6 months	1/year	1/year
Clinical status	General examination; developmental milestones; neurologic status including fine-motor skills; evaluation of movement disorder such as dystonia, chorea, tremor, muscle weakness, speech articulation; and reception, behavior, concentration, and development	Every 3 months	Every 6 months	1/year	1/year
Diet	Daily intake of lysine (mg/kg), natural protein and protein from AAM (g/kg); calories (kcal/kg); fat (g/kg)	Every 3 months	Every 6 months	1/year	1/year
Biochemistry	See Table 7	Every 3 months	Every 6 months	1/year	1/year
Neuroradiology	cMRI	At any neurologic deterioration (see Recommendation no. 16)			
Developmental parameters of motor and psychologic functions	Regular evaluation of intelligence, motor function, and speech/language (see Recommendation no. 17)		At 12 and 24 months BSID III /Denver-Scales; at 3 years WPPSI I-III; at 5 years WPPSI I-III	At 8 years WISC IV	At 18 years WISC IV
Quality of life	Separate assessment of quality of life for affected individuals and their parents		1/year		
Psychosocial counseling	Reimbursement of expenses for medication or travel, handicapped ID, etc.	At initial presentation	On request		

BSID III Bayley Scales of Infant and Toddler Development, Third Edition 2006, *cMRI* cerebral magnetic resonance imaging, *WPPSI Wechsler Preschool and Primary Scale of Intelligence*, Third Edition 2006, *WISC IV Wechsler Intelligence Scale for Children*, Fourth Edition, 2007

Clinical monitoring after head injury Even under recommended treatment and without macrocephaly, SDH may occur after minor head trauma (Zielonka et al. 2015).

	Recommendation no. 12
Recommendation for	Individuals with GA-I should be admitted to a hospital and closely monitored after head trauma.
Level of evidence	Low (SIGN level 3 to 4).
Clinical relevance	High.

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Biochemical monitoring

Organic acids Start of dietary treatment results in decreased urinary concentrations of GA and 3-OH-GA in high (Hoffmann et al. 1991, 1996; Strauss et al. 2003, 2011) but not in low (Greenberg et al. 2002) excreters. Urinary concentrations of GA and 3-OH-GA do not correlate with clinical parameters (Boy et al. 2013; Christensen et al. 2004; Couce et al. 2013; Kölker et al. 2006; Viau et al. 2012).

	Recommendation no. 13
Recommendation for	Analysis of urinary concentrations of GA and 3-OH-GA should not be used for treatment monitoring.
Level of evidence	Moderate (SIGN level 2+ to 3). Consistency of evidence is high.
Clinical relevance	Low.

GA glutaric aciduria type I, *3-OH-GA* 3-hydroxyglutaric acid, *SIGN* Scottish Intercollegiate Guidelines Network

Amino acids Quantitative analysis of plasma amino acids helps ensure that patients on a low-lysine diet are receiving a nutritionally adequate diet (Müller and Kölker 2004; Yannicelli et al. 1994). There is no clear-cut correlation between plasma lysine concentrations and lysine intake (Boy et al. 2013; Kölker et al. 2012), but lysine level should be maintained within the normal range. Tryptophan cannot be

measured accurately by conventional amino acid analysis; therefore, if tryptophan deficiency is clinically suspected, plasma tryptophan level should be measured using high-performance liquid chromatography (HPLC) or MS/MS (Krstulovic et al. 1977; Laich et al. 2002). Tryptophan deficiency has not been reported in individuals receiving lysine-free, tryptophan-reduced AAMs.

Recommendation no. 14	
Strong recommendation for	Infants and children on a low-lysine diet should have amino acids in plasma (ideally 3–4 h postprandially) quantified regularly. Concentrations of lysine and other essential amino acids should be maintained within the normal range.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is high.
Clinical relevance	High.

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Carnitine status Carnitine supplementation prevents secondary depletion of free carnitine and contributes to positive outcome (Bjugstad et al. 2000; Heringer et al. 2010; Hoffmann et al. 1996; Kölker et al. 2006, 2007a; Seccombe et al. 1986). Carnitine status in plasma can be assessed using HPLC or MS/MS analysis and provides information on adherence to treatment. MS/MS analysis of DBS may detect secondary carnitine depletion but is less precise than plasma analysis. Plasma carnitine concentrations are usually within the upper range of normal when given according to recommendations in Table 2 (Boy et al. 2013; Couce et al. 2013).

Recommendation no. 15	
Recommendation for	Carnitine level in plasma should be monitored regularly in all individuals with GA-I.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

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Acylcarnitine profile Although effective for NBS, regular assessment of C5DC and other acylcarnitines in DBS or serum does not provide relevant or reliable treatment monitoring information. For example, C5DC concentrations increase markedly with carnitine supplementation, regardless of lysine intake (Chace et al. 2003; Lindner et al. 2004; Wilcken et al. 2003).

Additional biochemical monitoring Analysis of other parameters, such as complete blood cell count, albumin, calcium, phosphorous, vitamin D, ferritin, and serum transaminases, may be helpful for routine surveillance, helping to detect insufficient intake of micronutrients or energy substrates (Ma et al. 2013a, b; Yannicelli et al. 1994). However, they are usually normal in individuals compliant with treatment recommendations during the first 6 years of life (Boy et al. 2013). Therefore, these parameters should only be analyzed if clinically indicated (Table 7).

Kidney function A recent study demonstrated chronic renal failure in some adolescent and adults with GA-I (Kölker et al. 2015b). Therefore, renal function should be monitored in adults with GA-I. Renal tubular dysfunction following a high-protein challenge was observed in the mouse model for GA-I (Thies et al. 2013).

Table 7 summarizes recommended best practices for minimal requirement for biochemical monitoring.

Biochemical monitoring during acute illness

Individuals with GA-I are at risk for dehydration and electrolyte imbalance during periods of recurrent vomiting, diarrhea, and/or reduced intake of nutrients and fluids, increasing the risk for an encephalopathic crisis (Bjugstad et al. 2000; Hoffmann et al. 1996; Kölker et al. 2006; Kyllerman et al. 2004; Strauss et al. 2003). Blood gases and serum electrolytes should be assessed on admission, and emergency treatment adjusted accordingly (see Table 5). Since single cases of rhabdomyolysis have been reported (Chow et al. 2003), monitoring of creatine kinase (CK) levels during a crisis is also recommended.

Neuroradiological monitoring

Cranial MRI studies have elucidated a characteristic pattern of gray and white matter abnormalities and widened CSF spaces in GA-I (Supplementary Table 3). However, striatal and extrastriatal MRI abnormalities are highly variable and dynamic (Harting et al. 2009). MRI with diffusion-weighted imaging allows earlier and more precise detection of striatal lesions than does computed tomography (CT) (Brismar and Ozand 1995; Desai et al. 2003; Elster 2004; Garbade et al. 2014; Lee et al. 2013; Kurtcan et al. 2015; Neumaier-Probst et al. 2004; Oguz et al. 2005; Strauss et al. 2007; Twomey et al. 2003; Viau et al. 2012). Cranial ultrasound can also detect structural brain abnormalities (Forstner et al. 1999) as early as last trimester of pregnancy (Lin et al. 2002). Although serial MRI scans may allow better understanding of neuropathogenesis by observing its temporal evolution, they are not considered essential for monitoring.

Three case reports on subependymal mass lesions have been published in individuals with a late-onset form of GA-I (Herskovitz et al. 2013; Korman et al. 2007; Pierson et al.

Table 7 Minimal requirements for biochemical monitoring

Parameter	Rationale	Frequency at age			
		0–1 years	1–6 years	>6 years	>18 years
Amino acids (plasma)	General nutritional status	Every 3 months	Every 6 months	Every 12 months	Every 12 months
Carnitine (plasma or serum)	Avoid depletion, check for non-adherence	Every 3 months	Every 6 months	Every 12 months	Every 12 months
Creatinine, cystatin-C, GFR	Kidney function			Every 12 months	Every 12 months
Complete blood count, calcium, phosphorous, albumin, transaminases, parathormone, alkaline phosphatase, vitamin B_{12}, iron status	General nutritional status, bone status[a]	At any clinical abnormalities, i.e., signs for malnutrition, failure to thrive, feeding problems.			

GFR glomerular filtration rate

[a] If inadequate bone mineralization is suggested, additional tests are required (e.g., radiological investigations for bone age and density)

2015), but a causal relationship of the underlying metabolic defect is unclear so far.

Recommendation no. 16	
Recommendation for	Neuroradiological investigation should be performed if signs of neurologic deteroriation occur.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is moderate.
Clinical relevance	Moderate to high.

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It has recently been demonstrated that intracerebral concentrations of neurotoxic metabolites GA and 3-OH-GA can be detected by noninvasive ^{1}H-MRS in vivo (Harting et al. 2015). It remains to be elucidated whether this method can be used for long-term monitoring and therapy adaptation.

Developmental diagnostics of motoric and psychologic functions

Comprehensive studies on cognitive functions in GA-I have not been reported. Given the characteristic cerebral abnormalities frequently observed in GA-I (Supplementary Table 3) and the impact of similar white matter changes observed in other neurologic diseases (Schmahmann et al. 2008), individuals with GA-I might be at risk for cognitive dysfunction. Therefore, regular evaluation of neuropsychological function is important. The generally held assumption that the intellect is spared in GA-I (Morton et al. 1991) is based on small case series without adequate control groups and using differing methodologies (Brown et al. 2015; Couce et al. 2013; Lee et al. 2013). Other studies have reported decreased IQ or subtle cognitive dysfunction in children with GA-I (Beauchamp et al. 2009; Boneh et al. 2008; Gupta et al. 2015; Lee et al. 2013; Yang et al. 2011), and cognitive decline has also been reported in individuals with late-onset GA-I (Külkens et al. 2005). A recent study demonstrated that analysis of information processing can be used to evaluate neuropsychologic functions in GA-I (Boy et al. 2015), but its relevance and role in long-term monitoring is unclear.

Monitoring psychologic functions should include intelligence (developmental quotient in young children) for assessing the general level of development, motor functions (including fine-motor skills), and language (Table 6). Early-intervention strategies can only be implemented after early detection of specific deficits.

Recommendation no. 17	
Recommendation for	Neuropsychologic functions, i.e., intelligence/developmental quotient, motor functions, and language, should be evaluated regularly to detect specific deficits early and allow initiation of appropriate intervention services.
Level of evidence	Moderate (SIGN level 2+ to 3). Consistency of evidence moderate.
Clinical relevance	High.

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Quality of life

Metabolic diseases have huge influence on everyday life (de Ridder et al. 2008; Gramer et al. 2014; Zeltner et al. 2016). Individuals with organic acidurias show more mental disability as well as behavioral and emotional problems. Assessment of psychosocial factors and quality of life (QoL) in affected individuals and their families is therefore an important part of long-term management. The impact of the disease may be a greater burden on the family than on the patient, particularly when patients are young. Consequently, the ability of the family to cope with the patient's illness can have

a significant impact on the patient's QoL (Jamiolkowski et al. 2016).

> **Statement no. 4:** Psychosocial effects of the diagnosis and treatment of GA-I should be assessed in both affected individuals and their families as part of routine monitoring.

General procedures for medical health care

No systematic studies have been performed to determine an optimal approach to medical management of GA-I (or other metabolic diseases). Based on the best clinical experience and knowledge of GDG, we recommend the following process:

After definite diagnosis (Fig. 1), the affected individual is initially admitted to an interdisciplinary metabolic center for a short inpatient stay. Families receive intensive informational consultation (including delivery of information materials) by a specialist for inherited metabolic diseases, aiming to form a common perspective on diagnosis, treatment, and prognosis. Metabolic maintenance therapy is initiated, and parents are intensively educated in dietary management and pharmacotherapy. Additionally, families receive psychosocial advice and emergency cards (or letters) providing details on emergency treatment and contact information of the metabolic center. Families should be instructed on how to recognize symptoms that indicate impending catabolism and be given a stepwise introduction to emergency treatment. Metabolic specialists will explain to families the importance of regular follow-up investigations, including their frequency and content. Use of interpreters may be required. Long-term management should be done in an interdisciplinary metabolic center in close cooperation with external childrens' hospitals (i.e., for emergency treatment), local general pediatricians (i.e., vaccinations, regular medical checkups), specialized outpatient departments, family support groups for individuals with GA-I (exchange of experience), and other entities, such as schools and daycare centers, important for ensuring the well-being of affected individuals. Translation of new research results into clinical management is an important part of the entire evaluation and treatment process.

Transition to adult medicine and long-term care

Transition of adolescents and young adults with metabolic diseases from pediatrics to adult medicine is essential for long-term management and should be organized as a well-planned, continuous, interdisciplinary process integrating all relevant players. Standardized procedures for transition do not exist (inter-)nationally due to the absence of interdisciplinary outpatient departments. However, some transitional care concepts have been developed in which adult internal specialists initially see individuals with GA-I together with pediatric metabolic experts, dietitians, psychologists, and social workers—and later on independently (Vom Dahl et al. 2014).

In puberty and early adulthood, deficits in adherence to treatment may occur due to noncompliance or other unknown factors resulting in negative impact on clinical outcome (Watson 2000). As the long-term course of pediatric metabolic diseases in this age group is unknown, continuous supervision by a metabolic center with sufficient personal and technical resources is essential.

Although details on neuropathogenesis and long-term outcome are still unclear in GA-I, knowledge has increased considerably since publication of the first guideline recommendations in 2007 (Kölker et al. 2007b). New discoveries in basic and clinical research as well as a better understanding of phenotype and natural history of GA-I have all led to improved outcomes. Five years ago, the first guideline revision was published (Kölker et al. 2011). For this second revision of proposed recommendations for the diagnosis and treatment of GA-I, new research findings, clinical experience, and expertise of the GDG, as well as the perspectives of affected individuals, have been integrated and hopefully will be accepted and implemented. However, future studies on long-term outcome, treatment monitoring, characterization of variant GA-I onset types, and methods for reliable detection of low excreters are necessary.

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