Year: 2021

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DOI: https://doi.org/10.1002/jimd.12335

Originally published at:
Märtner, E M Charlotte; Maier, Esther M; Mengler, Katharina; Thimm, Eva; Schiergens, Katharina A; Marquardt, Thorsten; Santer, René; Weinhold, Natalie; Marquardt, Iris; Das, Anibh M; Freisinger, Peter; Grünert, Sarah C; Vossbeck, Judith; Steinfeld, Robert; Baumgartner, Matthias R; Beblo, Skadi; Dieckmann, Andrea; Näke, Andrea; Lindner, Martin; Heringer-Seifert, Jana; Lenz, Dominic; Hoffmann, Georg F; Mühlhausen, Chris; Ensenauer, Regina; Garbade, Sven F; Kölker, Stefan; Boy, Nikolas (2021). Impact of interventional and non-interventional variables on anthropometric long-term development in glutaric aciduria type 1: A national prospective multi-centre study. Journal of Inherited Metabolic Disease, 44(3):629-638.
DOI: https://doi.org/10.1002/jimd.12335

Received: 7 October 2020 | Revised: 23 November 2020 | Accepted: 30 November 2020

DOI: 10.1002/jimd.12335

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Impact of interventional and non-interventional variables on anthropometric long-term development in glutaric aciduria type 1: A national prospective multi-centre study

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Abbreviations: 3OHGA, 3-hydroxyglutaric acid; (A)ET, (adherence to recommended) emergency treatment; (A)MT, (adherence to recommended) maintenance treatment; EC, encephalopathic crisis; GA, glutaric acid; GA1, glutaric aciduria type 1; GCDH, glutaryl-CoA dehydrogenase; HE, high excreter; IQR, interquartile range; LE, low excreter; MD, movement disorder; MRI, magnetic resonance imaging; NBS, newborn screening; SDS, SD score.

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Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: #01GM0305; Dietmar Hopp Foundation; European Union; Kindness for Kids Foundation

Communicating Editor: Sander M Houten

Abstract

Glutaric aciduria type 1 (GA1) is a rare neurometabolic disorder, caused by inherited deficiency of glutaryl-CoA dehydrogenase, mostly affecting the brain. Early identification by newborn screening (NBS) significantly improves neurologic outcome. It has remained unclear whether recommended therapy, particular low lysine diet, is safe or negatively affects anthropometric long-term outcome. This national prospective, observational, multi-centre study included 79 patients identified by NBS and investigated effects of interventional and non-interventional parameters on body weight, body length, body mass index (BMI) and head circumference as well as neurological parameters. Adherence to recommended maintenance and emergency treatment (ET) had a positive impact on neurologic outcome and allowed normal anthropometric development until adulthood. In contrast, non-adherence to ET, resulting in increased risk of dystonia, had a negative impact on body weight (mean SDS −1.07; $P = .023$) and body length (mean SDS −1.34; $P = -.016$). Consistently, longitudinal analysis showed a negative influence of severe dystonia on weight and length development over time ($P < .001$). Macrocephaly was more often found in female (mean SDS 0.56) than in male patients (mean SDS −0.20; $P = .049$), and also in individuals with high excreter phenotype (mean SDS 0.44) compared to low excreter patients (mean SDS −0.68; $P = .016$). In GA1, recommended long-term treatment is effective and allows for normal anthropometric long-term development up to adolescence, with gender- and excreter type-specific variations. Delayed ET and severe movement disorder result in poor anthropometric outcome.

KEYWORDS

anthropometrics, biochemical subtype, development, diet, dystonia, glutaric acidemia type 1, glutaric aciduria type 1, newborn screening

1 | INTRODUCTION

Glutaric aciduria type 1 (GA1; OMIM #231670) is a rare inherited neurometabolic disorder of L-lysine, L-hydroxylysine and L-tryptophan metabolism. It is caused by inborn deficiency of glutaryl-CoA dehydrogenase (GCDH; EC 1.3.8.6) resulting in accumulation of glutaryl-CoA and, subsequently, glutarylcarnitine (C5DC), glutaric acid (GA) and 3-hydroxyglutaric acid (3OHGA).

During the first months of life, untreated patients are usually asymptomatic or show transiently delayed motor development or muscular hypotonia.[1,2] Between 3-36 months of age, however, the majority of untreated individuals develops a complex dystonic movement disorder (MD) due to striatal injury precipitated by acute encephalopathic crises (EC) during febrile illness or other causes of catabolic state (acute onset), but in a relevant number of individuals MD manifests without apparent preceding crises (insidious onset). Two biochemical groups were distinguished based on the GA concentration in urine[3]: a high excreter (HE) phenotype in individuals with urinary GA concentrations ≥100 mmol/mol creatinine and a low excreter (LE) phenotype if the GA concentration is below this cut-off. Urinary 3OHGA is elevated in most patients and may be the only biochemical derangement of LE individuals, with much less variation than GA. Urinary GA excretion inversely correlates

with the GCDH residual enzyme activity, with HE individuals showing 0% to 2% and LE patients 3% to 30% of residual GCDH activity.[4] Both subtypes are thought to share the same risk for striatal injury during infancy. This is explained by intracerebral and intramitochondrial entrapment of neurotoxic dicarboxylic metabolites secondary to the lack of specific transporters for CoA esters (inner mitochondrial membrane) and dicarboxylic acids (blood-brain barrier), resulting in accumulation of these metabolites in vulnerable compartments[5,6] and bioenergetic impairment.[7,8] However, recent ^{1}H-MRS studies revealed higher intracerebral in vivo concentrations of neurotoxic metabolites and a higher frequency of magnetic resonance imaging (MRI) abnormalities in HE patients compared to LE patients.[1,4,9] The underlying mechanism remains to be elucidated; glutarylation of mitochondrial proteins, such as glutamate dehydrogenase, in astroglial cells might be involved.[10,11]

Implementation of GA1 into national newborn screening (NBS) programmes has significantly improved neurologic outcome, particularly in individuals following recommended therapy.[12-18] Evidence-based treatment guidelines, established and twice revised by an international guideline committee,[19-21] recommend low lysine diet, supplemented with lysine-free, tryptophan-reduced, arginine-fortified amino acid mixtures up to age 6 years and a relaxed protein-controlled diet for older patients, and additional lifelong oral carnitine supplementation for maintenance treatment (MT). Rapid start of emergency treatment (ET) in every potentially threatening episode that may precipitate catabolism is recommended in patients up to 6 years while efficacy in older patients is unclear.

Safety and anthropometric outcome of recommended dietary long-term treatment has not yet been prospectively studied in screened and early treated GA1 patients beyond the age of 6 years.[22] Therefore, the aim of this study is to investigate the long-term anthropometric and neurologic development of patients with GA1 up to adolescence and to evaluate the impact of interventional and non-interventional parameters on body weight, body length, body mass index (BMI) and head circumference as well as on neurologic outcome.

2 | METHODS

2.1 | Study population

This national multi-centre study is a prospective, non-randomised, non-controlled observational trial for patients with GA1. Inclusion criteria were (a) identification by NBS between 1 January 1999 and 1 July 2016 in Germany; (b) confirmation of diagnosis by quantitative analysis of urinary GA and 3OHGA and/or *GCDH* gene analysis and/or quantitative residual enzyme activity of GCDH; and (c) written informed consent from patients and/or parents. Patients who did not fulfil these criteria were excluded. All patients were included in a patient registry established and managed by the European registry and network for Intoxication type Metabolic Diseases (E-IMD; https://www.eimd-registry.org/).[23,24]

2.2 | Outcome variables

Anthropometric data, specifically body weight, body length, BMI and head circumference, and all therapeutic follow-up parameters were assessed prospectively. All anthropometric measurements were transformed into a SD score (SDS) using the LMS method and age-dependent standard values to assess and compare anthropometric development in different age groups.[25,26]

2.3 | Biochemical subtype

Biochemical subtypes were defined as previously described.[3] Urinary GA was <100 mmol/mol creatinine or even normal in LE patients and ≥100 mmol/mol creatinine in HE patients.

2.4 | Treatment and supervision by a specialised metabolic centre

Guidelines recommend the use of MT and ET, and supervision by a specialised metabolic centre.[21] MT consists of (a) age-adapted low lysine diet with supplementation of a lysine-free, tryptophan-reduced and arginine-fortified amino acid supplement until the age of 6 years; (b) protein-controlled diet avoiding products with high lysine content and excessive protein intake for patients older than 6 years; and (c) lifelong oral carnitine supplementation. ET consists of (a) high carbohydrate supply; (b) low to no protein intake; and (c) increased carnitine dose. ET should be started without any delay, that is, within 24 hours after the onset of alarming symptoms, and in every potentially catabolic situation such as febrile illness and surgery. Adherence to ET and MT was considered (AMT, AET) if all criteria listed above were fulfilled during the study interval. Supervision by a metabolic centre starting during the neonatal period and lasting until adulthood was prerequisite for being classified alike.

2.5 | Migration background

Migration background was defined by at least one parent being born neither in Germany nor a German-speaking (part of a) country such as Austria or Switzerland.

2.6 | Neurologic manifestations

Neurologic manifestations were classified depending on the presence and severity of a dystonic MD. Patients were classified as (a) asymptomatic in the absence of MD; (b) mildly affected if MD did not cause significant disability in daily life; (c) moderately affected if MD caused motor disability affecting daily life, but with some motor functions being preserved; and (d) severely affected if MD caused significant disability with few motor skills left.[12] Onset of dystonic MD was (a) acute with EC; or (b) insidious without an apparent crisis.

2.7 | Statistical analysis

Independent variables used for anthropometric outcome analysis were (a) severity of a dystonic MD; (b) biochemical subtype; (c) gender; (d) migration background; (e) adherence to MT; (f) adherence to ET; and (g) supervision by a specialised metabolic centre. Analyses were computed with the statistical package R.[27] In a cross-sectional analysis, welch two sample *t*-test was applied to evaluate effects of the aforementioned variables on anthropometric parameters. Variables with significant effects ($P < .1$) were selected for a linear model to assess interaction. A linear mixed model was used for longitudinal analysis of anthropometric development.

2.8 | Ethics approval

The Institutional Ethics Committee of the coordinating centre and all contributing study sites approved the study (University Hospital Heidelberg, application number S-525/2010).

3 | RESULTS

3.1 | Study sample and epidemiology

This study includes 79 patients (41 females, 38 males) with confirmed diagnosis of GA1 following identification by NBS. Detailed neurologic outcome was published separately.[13] Due to incomplete data sets, eight patients identified by NBS could not be included. The study population comprised 92% (59/64) of all GA1 patients identified by NBS in Germany and reported by the German National Society for Newborn Screening between January 2004 and July 2016. Median age at diagnosis was 7 days (range 2-217 days, interquartile range [IQR] 6-10 days) with a cumulative follow-up time of all patients of 663 years. Median age at last visit was 8.77 years (range 0.77-17.75 years, IQR 4.18-12.66 years) with 66 patients (84%) being older than 3 years and 49 patients (62%) older than 6 years at last visit. Seventy patients (89%) were regularly followed by a specialised metabolic centre, while nine patients (11%) were followed by local paediatricians and children's hospitals without metabolic focus. Fifty-nine patients (75%) had HE phenotype whereas 18 patients (23%) were classified as LE. For two genetically confirmed patients the biochemical phenotype was not reported. Thirty-seven patients' parents (47%) were born in Germany, and 42 patients (53%) had a migration background. Up to age 6 years, adherence to MT recommendations for calculated diet and carnitine supplementation was documented in 23/30 patients (77%), while seven patients did not follow the recommendations (23%). After the age of 6 years, MT was adequate in 39/49 patients (80%) with 29 patients (59%) following the recommendations for protein-controlled diet and 10 patients (20%) continuing calculated diet whereas 10 patients (20%) had no diet. In total, AMT was found in 62 patients (78%; vs no AMT n = 17 [22%]). Reasons for non-adherence to MT were non-compliance to the diet (n = 8), feeding problems (n = 1), delayed start of MT (n = 2) or inadequate dietary prescription (n = 6). Seventy patients (89%) received AET before the age of 6 years, while it was started with significant delay in nine patients (11%).

3.2 | Neurologic outcome

None of the patients showed irreversible neurologic symptoms at time point of diagnosis, and at last visit, the majority of patients (n = 53; 67%) still had not developed motor symptoms. Twenty patients (25%) suffered from a dystonic MD, n = 1 (1%) showed ataxia, while n = 5 (6%) had minor neurologic abnormalities such as fine motor deficits. Onset type of MD was acute following EC in nine cases (45%) and insidious in 11 cases (55%). Dystonia was mild in eight patients, moderate (n = 7) or severe (n = 5) at last visit. During prospective follow-up, degree of MD remained unchanged in 14 patients, whereas aggravation was found in five patients (of which four had insidious onset) and improvement in one. During the observational period, none of the patients developed major or minor motor symptoms *after* the age of 6 years. Impact of

treatment quality on neurologic long-term outcome was published previously.[13]

3.3 | Anthropometric outcome

Table 1 and Supporting Information Table S1 summarise all anthropometric data collected at last visit, with SDS indicating deviations from age group references. In brief, body weight (mean SDS −0.09; SD 1.38), body length (mean SDS −0.32; SD 1.29), BMI (mean SDS 0.13; SD 1.27) and head circumference (mean SDS 0.17; SD 1.47) were within the reference range indicating age-appropriate long-term development. In an additional longitudinal analysis, development of SDS was analysed for weight (26 patients), length (25 patients), BMI (25 patients) and head circumference (22 patients) showing no age-dependent effects over time.

Next, we evaluated effects of interventional and non-interventional variables on anthropometric long-term development. Detailed data can be found in Supporting Information Table S1.

3.4 | Effects of non-interventional parameters

3.4.1 | Dystonic movement disorder

Asymptomatic patients and those with mild and moderate MD showed normal development of weight up to late adolescence (mean SDS −0.06, 0.53 and −0.26 respectively; Figure 1). In contrast, individuals with severe dystonia had an impaired weight gain (mean SDS −1.45; $F[3,238] = 20.42$; $P < .001$). Results for body length were similar with asymptomatic and mildly affected patients showing normal growth over time (mean SDS 0.01 and 0.66 respectively). In contrast, longitudinal growth was impaired in individuals with moderate and severe dystonia (mean SDS −0.76 and −0.94 respectively; $F[3,238] = 7.55$; $P < .001$; Supporting Information Figure S1).

3.4.2 | Biochemical subtype

At last visit, patients with HE phenotype had a larger head circumference (mean SDS 0.44) compared to patients with LE phenotype (mean SDS −0.68; $P = .021$, Figure 2). The effect was confirmed in a linear model ($P = .016$), but less pronounced in a longitudinal analysis (mean SDS 0.73 and −0.58 respectively; $P = .089$), however, including less patients (n = 22). Exclusion of the two outliers (which, however, were confirmed by multiple validation) from analysis had an impact on the level of significance (mean SDS in LE patients −0.17; $P = .051$ and $P = .171$ in the linear model). Development of body weight, body length and, subsequently, BMI did not differ between HE and LE patients.

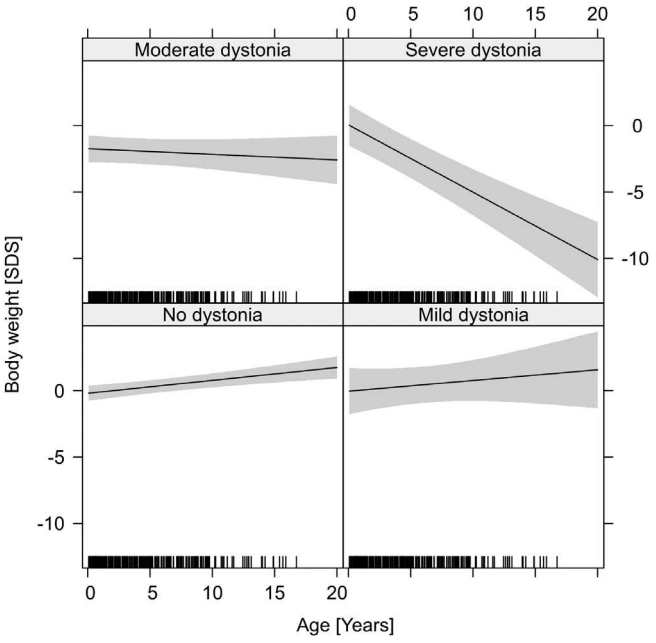

FIGURE 1 Severity of dystonia and development of body weight (SDS). Development of body weight was normal in asymptomatic patients and those with mild or moderate dystonia, but impaired in those with severe dystonia ($F[3,238] = 20.42$; $P < .001$). SDS, SD score

TABLE 1 Anthropometric data of the study population at last visit

Anthropometric parameter	n	Mean SDS	SD	Q1	Median	Q3	Minimum	Maximum
Body weight	79	-0.09	1.38	−0.66	0.09	0.65	−5.19	3.11
Body length	79	−0.32	1.29	−0.93	−0.28	0.53	−5.74	2.31
BMI	79	0.13	1.27	−0.64	0.21	0.82	−2.89	3.08
Head circumference	51	0.17	1.47	−0.69	0.03	1.42	−3.55	3.46

Note: All parameters are within the reference range.

Abbreviations: BMI, body mass index; n, number of patients; SDS, SD score.

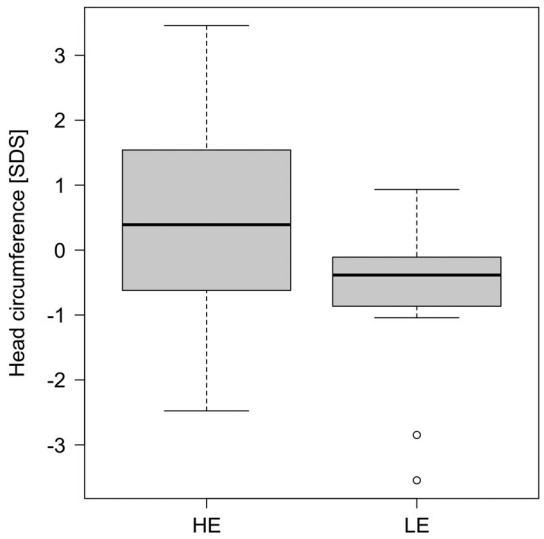

FIGURE 2 Biochemical subtype and head circumference (SDS) at last visit. Head circumference in HE patients (mean SDS 0.44) was increased compared to LE patients (mean SDS −0.68; $P = .016$). HE, high excreter; LE, low excreter; SDS, SD score

3.4.3 | Gender

Increased head circumference was more pronounced in female (mean SDS 0.56) than in male patients (mean SDS −0.2; $P = .067$; Supporting Information Figure S2), which was confirmed in a linear model including biochemical subtype and gender ($P = .049$). In contrast, SDS for body weight, body length and BMI did not differ.

3.4.4 | Migration background

Migration background had no impact on anthropometric development.

3.5 | Effects of interventional parameters

3.5.1 | Maintenance treatment

Treatment quality has the strongest impact on neurologic outcome in a screened population, a notion supported by 93% of patients, who adhered to MT and ET, having remained asymptomatic.[13] In contrast to the negative effect on neurologic outcome, however, non-adherence to MT had no significant direct impact on anthropometric development. Mean SDS for weight was 0.01 for patients with AMT and −0.44 for patients without ($P = .303$). Results for length (mean SDS −0.30 [AMT] vs −0.41 [no AMT]; $P = .738$), BMI (mean SDS 0.24 [AMT] vs −0.24 [no AMT]; $P = .243$) and head circumference (0.25 [AMT] vs −0.04 [no AMT]; $P = .583$) did not differ (Supporting Information Figure S3).

3.5.2 | Emergency treatment

Delayed ET results in strongly increased risk of acute onset and mainly severe dystonic MD.[13] Accordingly, non-adherence to ET had a significantly negative impact on body length (mean SDS −1.34 [no AET] vs −0.19 [AET]; $P = .018$) and also tended to impair body weight (mean SDS −1.07 [no AET] vs .04 [AET]; $P = .082$; Figure 3). Both effects were confirmed and significant in a linear model with $P = .016$ (body length) and $P = .023$ (body weight). Of note, since delayed ET and severe dystonia were associated, effects may also reflect impact of MD. AET did not affect BMI and head circumference.

3.5.3 | Supervision by a metabolic centre

Patients not followed by a metabolic centre showed a trend towards impaired body length (mean SDS −0.83 vs −0.26; $P = .073$), which, however, was not confirmed in a linear model including AET and supervision by a metabolic centre ($P = .333$). Body weight, BMI and head circumference did not differ between these patients.

4 | DISCUSSION

The major findings of this study investigating the long-term anthropometric development of 79 individuals with GA1 identified by NBS in Germany between 1999 and 2016 are (a) MT according to guideline recommendations allows normal anthropometric development and prevents malnutrition up to adolescence in all but severely affected patients; (b) adherence to ET is crucial for both neurologic and anthropometric outcome; (c) severity of dystonic MD has a strong impact on anthropometric long-term development; and (d) head circumference is more pronounced in patients with HE phenotype as well as in female patients.

4.1 | Dietary management according to guideline recommendations is safe

Until now, effects and safety of recommended dietary treatment for GA1 have not been evaluated for adolescent or adult patients, but was shown to be safe up to

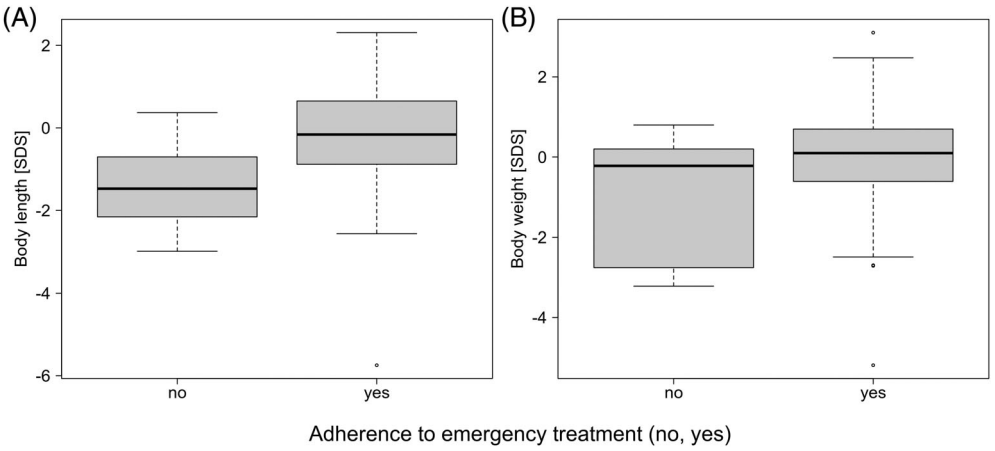

FIGURE 3 Effect of adherence to emergency treatment and body length (A; SDS), body weight (B; SDS) at last visit. Delayed or no AET had a negative impact on body length (A; mean SDS −1.34 [no AET] vs −0.19 [AET]; $P = .016$) and body weight (B; mean SDS −1.07 [no AET] vs 0.04 [AET]; $P = .023$). AET, adherence to emergency treatment; SDS, SD score

the age 6 years in treated patients.[22,28] According to the guideline, lysine intake should continue to be limited after age 6 years due to the uncertain neurologic and extra-neurologic long-term disease course including kidney dysfunction in adolescent patients,[23] reports on progredient extrastriatal abnormalities such as white matter disease, subependymal nodules or CNS tumours[9,29] and progredient clinical course in lately diagnosed patients.[30] However, the guideline recommends a relaxation of dietary treatment after the age of 6 years changing from the low lysine to a protein-controlled diet since striatal injury has not been demonstrated after the age of 6 years,[1] and current therapeutic concepts do not stop or slow extrastriatal MRI abnormalities that are regularly found especially in patients younger age 6 years with HE phenotype treated with low lysine diet.[31] Since safety and efficacy of protein-controlled diet has not yet been studied in detail for this age group, the risk of malnutrition with potentially negative impact on long-term anthropometric development and other clinical outcomes has remained unknown. Here, we show that recommended MT is safe until adolescence and early adulthood ensuring normal growth and preventing malnutrition in the vast majority of patients. None of the patients developed new major or minor motor symptoms after the age of 6 years demonstrating that protein-controlled diet after the age 6 years is effective and promotes favourable neurologic outcome, however, long-term impact of dietary treatment, especially on unclear outcome domains such as extrastriatal[9] or renal[23,24] abnormalities remains to be elucidated. Noteworthy, deviations of MT from current recommendations being associated with an increased risk to develop insidious onset MD[13] did not directly impair anthropometric outcome. However, adherence to MT is crucial and neurologic outcome was superior in patients showing full adherence to MT recommendations.[13]

4.2 | ET is crucial: Severe dystonia is the major risk factor for poor anthropometric outcome

Adherence to recommended ET is essential to prevent acute onset MD, which is often severe and results in reduced life expectancy and increased mortality.[1,2,13] Consistent with the findings of a previous study focussing on short-term outcome, patients with severe MD are at risk for strongly impaired anthropometric long-term development.[22] Our study shows that this impairment progresses continuously with age until adolescence and adulthood highlighting the need for intensive supervision and adaption of protein, calories and micronutrient intakes, individualisation of treatment plans or (intermittant) tube feeding if necessary. Affected patients may have increased energy demand despite immobility or even reduced energy demand[32] and should therefore be monitored carefully. As severely affected patients often also suffer from orofacial dyskinesia,[33] special interdisciplinary care and nutritional concepts are necessary to assure adequate nutrition in these patients.

4.3 | Impact of neurotoxins: HE phenotype as a risk factor for macrocephaly

The neurotoxic metabolites glutaryl-CoA, GA and 3OHGA are thought to play an important role in the pathophysiology of GA1. GA interferes with anaplerotic transport processes between astrocytes and neurons,[34] and 3OHGA is thought to interfere with glutamatergic and GABAergic neurotransmission,[35] and induces brain energy impairment and increased generation of reactive oxygen species.[7,36-38] Besides, cerebrovascular changes resulting in altered autoregulation and cerebral venous hypertension subsequently increase the risk for haemorrhages.[39,40] Concentrations of neurotoxic metabolites can be

modulated by the amount of lysine intake: While high oral lysine intake leads to increased cerebral concentrations of GA and subsequently to irreversible neurologic damage in *Gcdh*-deficient mice,[41] a low lysine diet reduces cerebral concentrations of neurotoxic metabolites significantly.[42,43] In spite of different peripheral concentrations of neurotoxins in urine or blood, post-mortem studies showed a massive intracerebral accumulation of GA and 3OHGA in both, HE and LE patients.[44] This was explained by intracerebral de novo synthesis and entrapment of neurotoxic metabolites due to a limited permeability of the blood-brain barrier for dicarboxylic acids.[5] Consistent with this, HE and LE patients are thought to share the same clinical course, that is, the same risk of developing acute EC and dystonic MD,[1,4] which also was confirmed in our study cohort before.[13] In addition to a similar neurological motor outcome, HE and LE patients also show the same risk for decline in kidney function over time.[13] However, in vivo brain metabolic profiles are different in HE and LE patients revealing normal concentrations of GA in LE patients, but significantly increased concentrations in HE patients.[9] Moreover, extrastriatal MRI abnormalities such as frontotemporal hypoplasia, widening of sylvian fissures or white matter abnormalities are more frequent in HE than in LE patients.[9,30] Of note, all three reported individuals developing CNS tumours were HE patients.[29] However, clinical consequences of these observations remain unclear. This is the first study revealing a *clinical* impact of biochemical subtypes in GA1 with HE patients showing a significantly larger head circumference than LE patients. This also might explain why the vast majority of patients suffering from subdural haemorrhage are HE patients while only one case of a LE patient was reported.[39,45,46] Nevertheless, impact of biochemical subtype on clinical outcome and long-term development remains to be elucidated.

In line with this, the interesting finding of larger head circumference in female compared to male patients that we observed should be investigated in further studies. In healthy children up to the age of 7 years, similar development of head circumference for boys and girls has been reported.[47] Until now, no differences regarding concentrations of metabolites, proportions of biochemical subtypes or clinical outcome between female and male GA1 patients have been published, nor has it been demonstrated in this study. This finding should be further investigated by future GA1 studies focussing on biochemical and clinical long-term disease course as well as neuroradiologic and MRI patterns.

4.4 | Study limitations

First, a multi-centre study assessing anthropometric data in children followed by numerous different metabolic centres or hospitals has to admit possible measurement inaccuracies. Second, there is no recently published reference population available for patients with migration background but the reference population published by Cole et al was assessed as an adequate reference since a relevant proportion in this study had a migration background.[26] Third, as a detailed analysis of laboratory data was not possible due to insufficient data quality, malnutrition could only be evaluated clinically, and not biochemically.

In summary, this study shows that treatment according to guideline recommendations in GA1 is safe and ensures normal anthropometric development up to adolescence with gender- and excreter-specific variations, while delayed ET with concomitantly severe MD is the major cause of poor anthropometric outcome in screened individuals with GA1.

ACKNOWLEDGMENTS

The authors thank the patients and their families for their participation in this study, and particularly the German parents group "Glutaric aciduria e.V." (URL: www.glutarazidurie.de). The study was supported by grants from the German Ministry of Education and Research (BMBF; Metabnet; #01GM0305; 2003–2006); Kindness for Kids Foundation (GAIN: 2006–2008 and GAIN2: 2009–2010), Munich, Germany; European Union (E-IMD; 2011–2014); Dietmar Hopp Foundation, St. Leon-Rot, Germany (LZO: 2005–2009 and NGS 2020: 2015–2020). None of the sponsors, did at any time influence the design and conductance of the study, nor did they influence data analysis, interpretation and publication of results. Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

AUTHOR CONTRIBUTIONS

Stefan Kölker initiated the study. E. M. Charlotte Märtner, Esther M. Maier, Katharina Mengler, Stefan Kölker and Nikolas Boy contributed to the conception and design of the study. E. M. Charlotte Märtner, Esther M. Maier, Katharina Mengler, Eva Thimm, Katharina A. Schiergens, Thorsten Marquardt, Natalie Weinhold, Iris Marquardt, Anibh M. Das, Peter Freisinger, Sarah C. Grünert, Judith Vossbeck, Robert Steinfeld, Matthias R. Baumgartner, Skadi Beblo, Andrea Dieckmann, Andrea Näke, Martin Lindner, Jana Heringer-Seifert, Dominic Lenz, Georg F. Hoffmann, Chris Mühlhausen, Regina Ensenauer, Sven F. Garbade, Stefan Kölker and Nikolas Boy contributed to the acquisition and analysis of data. E. M. Charlotte Märtner, Esther M. Maier, Stefan Kölker

and Nikolas Boy contributed to drafting the text and preparing the figures.

INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. The Institutional Ethics Committee of the coordinating centre and all contributing study sites approved the study (University Hospital Heidelberg, application number S-525/2010).

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SUPPORTING INFORMATION

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How to cite this article: Märtner EMC, Maier EM, Mengler K, et al. Impact of interventional and non-interventional variables on anthropometric long-term development in glutaric aciduria type 1: A national prospective multicentre study. *J Inherit Metab Dis*. 2021;1–10. https://doi.org/10.1002/jimd.12335