Diagnosis and management of glutaryl-CoA dehydrogenase deficiency

Glutaryl-CoA dehydrogenase (GCDH) deficiency is a rare inborn error of lysine, hydroxylysine and tryptophan metabolism which is treatable. If not diagnosed and treated timely this disease is devastating for most patients. It often manifests as acute encephalopathic crises during infancy and early childhood resulting in irreversible cerebral damage. A service for children and adults with GCDH deficiency should include a team of specialists with skills and interest in the management of inborn errors of metabolism.

DIAGNOSIS

The diagnostic guideline for GCDH deficiency is reflecting current best practice. However, no responsibility can be taken for missed diagnoses or failure of treatment.

► DIFFERENTIAL DIAGNOSIS

There is a wide differential diagnosis of macrocephaly, acute encephalopathy, basal ganglia injury, leukoencephalopathy, movement disorders, and subdural and retinal haemorrhages.

☑	The correct classification of GCDH deficiency has important practical implications when devising individual treatment plans and giving appropriate information to children and families and thus diagnostic work-up should be performed by metabolic specialists.

► NEONATAL AND HIGH-RISK SCREENING, AND CONFIRMATION OF DIAGNOSIS

Neonatal screening (if *a priori* risk is standard) and high-risk screening (if *a priori* risk is known to be increased) for GCDH deficiency is a *conditio sine qua non* for the best outcome.

☑	For neonatal screening for GCDH deficiency tandem mass spectrometry (MS/MS) should be used to detect glutarylcarnitine (C5DC) in dried blood spots (DBS).
☑	In a cohort of *low* excretors with a *high* carrier frequency and a *known GCDH* gene mutation, neonatal high-risk screening by MS/MS may produce a false negative result. Screening of these cohorts should consider alternative methods, such as DNA-based screening in DBS.
☑	For the confirmation of a positive neonatal screening result, a specific diagnostic work-up is required, including a quantitative analysis of glutaric and 3-hydroxyglutaric acids in urine, mutation analysis, and enzyme analysis.

► SELECTIVE SCREENING

☑	If clinical, neuroradiological or biochemical signs or symptoms are present that increase the *a priori* risk for GCDH deficiency, a specific diagnostic work-up should include analysis of glutaric and 3-hydroxyglutaric acids in urine, *GCDH* gene mutation analysis, and enzyme analysis.

MANAGEMENT

In this guideline the efficacy and safety of treatment strategies for GCDH deficiency have been reviewed using the best available evidence. However, an individualization of treatment may be necessary in case of weight loss, malnutrition, feeding problems or adverse effects of therapy.

► METABOLIC MAINTENANCE TREATMENT

DIETARY TREATMENT

☑	The prescription of any dietary treatment or medication requires an assessment of risk and of benefit. It may be necessary to adjust the treatment to meet individual needs in case of weight loss, malnutrition, feeding problems or adverse effects of therapy. To sucessfully cope with these problems, dietary treatment and pharmacotherapy should be implemented by an interdisciplinary team including metabolic pediatricians, dieticians, nurses and occupational therapists. Parents and patients should have regular training including written information on dietary treatment to minimize the risk of dietary mistakes.
☑	Any alternative approach to dietary treatment in GCDH deficiency that does *not* fulfil the international dietary recommendations is *not* recommended and should be considered as potentially dangerous.

C	**Lysine (Lys)-restricted dietary treatment (ie restriction of Lys to minimum requirements plus supplementation of Lys-free amino acids [AA] mixtures) is recommended for the metabolic maintenance treatment of GCDH deficiency, in particular in pre-symptomatically diagnosed patients up to age 6 years.**
☑	Lys-free amino acid mixtures, preferably reduced in tryptophan (Trp) and supplemented with essential nutrients and minerals, should be used for dietary treatment.
☑	**Dietary treatment after age 6 years:** Avoid excessive intake of natural protein. Natural protein with a low Lys content should be preferred. Addition of essential nutrients should be considered, particularly if there are feeding problems.
☑	**Children with feeding problems: 1. General recommendations.** Monitor growth and intake of essential nutrients. Keep the head in the midline position in dystonic patients to allow maximal mobility. Consider tube and overnight feeding. **2. Children with mild to moderate feeding problems.** Use semi-solid food (based on cereals, potatoes, milk, soy, vegetables, fruit), enrich food with protein-free formula powder (is already added with micronutrients) or use maltodextrin, cream and/or vegetable oil. Alternatively, protein-free high energy drinks can be administered as nutritional supplements. Increase the frequency and reduce the quantity of single meals. **3. Children with severe feedings problems.** Intensify the management (see 2). Reduce the volume of solid food (by increasing the concentration), concomitantly increase the quantity of fluids (preferably protein-free high-energy fluids). Solid food and fluids should be served separately. Implement a late meal. **4. Children with severe vomiting.** (See 2). Consider pharmacotherapy. Consider fundoplication or jejunostomy.

PHARMACOTHERAPY

C	**L-Carnitine should be supplemented in all patients and should be continued lifelong.**
☑	To prevent or reverse secondary carnitine depletion, an initial dosage of 100 mg L-carnitine/kg/d p.o. should be used and then should be adjusted to the concentration of free L-carnitine in plasma which should be kept in the normal range. Usually, carnitine supplementation can be reduced to 50 mg/kg/d p.o. in children (>6 years). A reduction of L-carnitine should be considered carefully if side effects, such as diarrhea and fish odour smell, occur.
C	**Riboflavin should be administered only if riboflavin responsiveness has been proven.**
D	**Drugs with unproven neuroprotective effect for GCDH deficiency (eg antiepileptic drugs, glutamate receptor antagonists, creatine monohydrate, antioxidants) should not be used for the maintenance treatment of affected patients.**

► EMERGENCY TREATMENT

D	**The following basic principles should be used for emergency treatment: Reverse catabolic state by administration of high-energy fluids (plus insulin). Reduce organic acid production by transient reduction or omission of natural protein. Continue to give Lys-free AA mixtures if at all possible. Amplify physiologic detoxifying mechanisms by carnitine supplementation and alkalination of urine. Prevent secondary carnitine depletion by carnitine supplementation. Balance body fluids and pH state by rehydration and buffering.**
C	**Emergency treatment should start without delay and should be performed aggressively during febrile illness, surgery and immunisation within the vulnerable period for acute encephalopathic crises (up to age 6 years).**
☑	Emergency treatment in children after age 6 years should be considered at least during severe diseases. It should be performed similarly to that in the age group 0-6 years with individual adaptation.

► MANAGEMENT OF MOVEMENT DISORDERS

☑	In all patients with GCDH deficiency, expert neurological evaluation should be performed by a neuropediatrician and/or later on by a neurologist to identify clearly the kind of movement disorder. In addition, dietitians, physicotherapists, occupational therapists, orthopediatrics, seeting and speech specialists, and providers of communication aids, should be consulted to enable multi-professional support for children with movement disorders.
D	**The benefit of affected patients from pharmacotherapy is uncertain. Baclofen and diazepam as monotherapy or in combination should be used as first line drug treatment for focal and generalized dystonia. Intrathecal baclofen should be considered as additional therapy for severe dystonia and spasticity.**
D	**Trihexyphenidyl should be considered a second line treatment for dystonia, in particular in adolescents and adults.**
D	**Botulinum toxin A should be considered as additional therapy for severe focal dystonia.**
D	**Antiepileptics, L-DOPA and amantadine should not be used for the therapy of movement disorders in GCDH deficiency.**
D	**The long-term benefit of dystonic patients from pallidotomy is uncertain. Pallidotomy should only be considered as part of a research project, not routine therapy.**

► ANTIEPILEPTIC DRUG TREATMENT

☑	Diagnosis, choice of antiepileptic drug therapy and management of seizures in GCDH deficiency should follow existing guidelines (eg SIGN guideline # 81: Diagnosis and management of epilepsies in children and young people). Since the confirmation and classification of epilepsies has important practicable implications, the diagnosis of epilepsy and choice of antiepileptic drugs should be made by a pediatric neurologist or pediatrician with expertise in childhood epilepsy.
☑	Valproate should be avoided for antiepileptic drug therapy since it may enhance mitochondrial dysfunction and carnitine depletion.

► SUBDURAL BLEEDINGS AND ARACHNOID CYSTS

D	**Children with subdural bleeding and/or bitemporal arachnoid cysts should be investigated for GCDH deficiency, in particular if occuring in combination with macrocephaly and/or movement disorders.**
D	**GCDH deficiency should be excluded in children with suspected shaken baby syndrome.**
D	**Neurosurgical interventions of arachnoid cysts and subdural bleedings in affected patients should be decided very cautiously and should be limited to acute life-threatening complications of increased intracranial pressure or of a midline shifting.**
☑	The metabolic management during and after surgical interventions should be supervised by a metabolic specialist to decrease the risk of acute encephalopathic crises.

► MONITORING

☑	At present, there is no reliable marker that predicts the outcome of GCDH deficiency.
☑	Therapy in diagnosed children with GCDH deficiency should be accompanied by regular professional monitoring which should be performed by a team of specialists. During the first year of life, clinical monitoring should be performed monthly (or at least bi-monthly), from age 1 to 6 years quarterly, and after age 6 years on a half-yearly (or at least yearly) basis. Monitoring should be re-inforced at any age if non-compliance, disease- or therapy-dependent complications have been newly detected.
☑	Analysis of urinary excretion of glutaric and 3-hydroxyglutaric acids should be used to assess the primary biochemical response of patients (high excretors) to dietary treatment and to evaluate riboflavin sensitivity, however, should not be considered for regular long-term follow-up investigations.

D	**Amino acids in plasma (fasting or at least 4 h postprandially) should be monitored during dietary treatment.**
☑	Trp should be monitored by HPLC or MS/MS analysis, in particular in patients receiving Lys- and Trp-free amino acid mixtures and children with feeding problems who have a higher risk for Trp depletion.
D	**Carnitine status in plasma should be monitored to detect secondary carnitine depletion.**
☑	Neuroradiologic investigations should be performed in case of neurologic deteroriation. To reduce sedatives in newborns and infants, neuroradiological investigations should be performed within physiological sleeping times, most preferably after feeding.

Diagnosis and management of glutaryl-CoA dehydrogenase deficiency

October 2005

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case control or cohort studies High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Evidence from expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 and 4; or Extrapolated evidence from studies rated as 2^{+}.

GOOD PRACTICE POINTS

☑ Recommended best practice based on the clinical experience of the guideline development group

1 Introduction

1.1. THE NEED FOR A GUIDELINE

Glutaryl-CoA dehydrogenase (GCDH, EC. 1.3.99.7) deficiency (synonym, glutaric acidemia or aciduria type I) is a rare autosomal recessive disease with an estimated prevalence of 1 in 100,000 newborns.[1] The *GCDH* gene is localized on chromosome 19p13.2 and encodes an FAD-dependent mitochondrial matrix protein that is involved in the degradative metabolism of L-lysine, L-hydroxylysine and L-tryptophan.[2-4] The *GCDH* gene which contains 11 exons and spans 7 kb is located on chromosome 19p13.2.[2] More than 150 disease-causing mutations are known.[5-9] R402W is the most frequent mutation in Caucasians. Some mutations are frequently or even exclusively found in certain countries or cohorts. Biochemically, GCDH deficiency is characterized by an accumulation of organic acids, ie glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and corresponding carnitine and glycine esters, ie glutarylcarnitine and glutarylglycine. These can be detected in body fluids (urine, plasma, CSF) and tissues by gas chromatography/mass spectrometry (GC/MS) or electrospray-ionization tandem mass spectrometry (MS/MS).[10-17] Two biochemically defined subgroups of patients have been described based on the highly variable urinary metabolite excretion, ie *low* excretors (glutaric $acid_{urine}$ <100 mmol/mol creatinine) and *high* excretors (glutaric $acid_{urine}$ >100 mmol/mol creatinine) – both of them presenting with the same but variable clinical phenotype.[5,7,10]

Since the description of two index patients in 1975 by Goodman and coworkers[18] more than 400 patients have been identified worldwide.[13,19-31] Three genetic isolates with a high carrier frequency (up to 1:10) and over-representation of this disease have been identified, including the Old Order Amish Community in Lancaster County, Pennsylvania, U.S.A.,[29,31] the Oji-Cree Indians in northeastern Manitoba and northwestern Ontario, Canada,[21,22] and the Irish travellers in the Republic of Ireland and United Kingdom.[27,28,30] If untreated, neurologic disease manifests in most patients during a finite period of brain development (age 3-36 months) by an encephalitis-like, acute encephalopathic crisis which is often precipitated by febrile illness, immunisation, or surgical intervention.[5,13,19,21-29,31] The characteristic neurological sequel of these crises is a bilateral striatal damage and, subsequently movement disorder. The clinical picture of the *"extrapyramidal"* syndrome may include focal, segmental, and generalized dystonia, orofacial dyskinesia, choreoathetotic movements, dysarthria, and a certain degree of spasticity superimposing on the extrapyramidal signs. Different types of extrapyramidal movements may be present at the same time, with one type often dominating the clinical picture (ie dystonia over dyskinesia). Dystonia is mostly the dominant extrapyramidal symptom, often accompanied by spasticity.[13,23-26,29] Morbidity and mortality is high in patients who have had a crisis.[24,26,29] In a few patients, neurologic disease has been demonstrated in the absence of any documented encephalopathic crises and has been termed *insidious-onset* type[5,23,24] and *late-onset* type.[32-35] It is not yet known whether this reflects an alternative pattern of disease in a subgroup of patients or underlying chronic neurodegeneration.

During the last three decades attempts have been made to establish and optimize therapy for GCDH deficiency. Dietary treatment (lysine- or protein-restriction; lysine-free, tryptophan-reduced amino acid supplements) in combination with oral supplementation of L-carnitine and – less frequently – riboflavin during maintenance treatment, and an intensified emergency treatment during episodes of intercurrent illness are used for the majority of patients. This treatment strategy has reduced remarkably the frequency of acute encephalopathic crises and thus morbidity and mortality in early diagnosed patients. Therefore, GCDH deficiency should now be considered to be a treatable condition.[23,24,27-29]

Clinical information on this disease is still limited and mostly based on observational experience from case reports and cohort studies, enrolling at maximum 77 patients. A review on these studies has evaluated 42 articles summarizing 115 patients.[19] Recently, an international cross-sectional study has been performed in 279 patients to evaluate systematically treatment efficacy and outcome in this disease.[24] The major results of this study were as follows: 1) Acute encephalopathic crises: The risk of acute encephalopathic crises precipitated by febrile intercurrent illness and immunisation is during a narrow timespan (age 0-70 months; median of first crisis: 9 months) and, subsequently, the severity of the striatal damage and dystonic movement disorders determines the prognosis. Most patients had only one single crisis. Only a minority of patients (6%) had no or only subtle neurologic abnormalities after a crisis. 2) Morbidity and mortality: Those patients who had had a crisis had a reduced life expectancy. Loss of mobility and feeding problems due to dystonia and orofacial dyskinesia were the most important sequels of encephalopathic crises. Furthermore, seizures and respiratory problems

induced by recurrent aspirations pneumonias were frequently found. Multiple morbidity was over-represented in deceased patients. 3) Diagnosis: The outcome was much improved in those in whom an early diagnosis was made, either by neonatal screening or by high-risk risk screening of extended families. 4) Treatment: A combination of lysine restriction (including supplementation of lysine-free, tryptophan-reduced amino acid mixtures) and oral carnitine supplementation improved the outcome, whereas riboflavin and protein restriction have no beneficial effect.

Early diagnosis based on clinical parameters is hampered by the lack of a characteristic or even pathognomonic clinical presentation before an encephalopathic crisis. (Progressive) macrocephaly is found in 75-80% of patients and is most pronounced during infancy, but is non-specific.[13,19,23,24,26,29,36] Since the late 1990s screening for GCDH deficiency has been included into some expanded MS/MS-based neonatal screening programmes (eg Germany, Australia, parts of U.S.A.) and a few screening programmes established for high-risk communities (Amish, Irish Travellers [Republic of Ireland]) enabling diagnosis of GCDH deficiency in neonates and thus reducing the *a priori* risk of patients for the manifestation of acute encephalopathic crises.[1,11,12,14,15,37-39] In Germany, GCDH deficiency has recently been included in the regular MS/MS-based neonatal screening (since April 1, 2005). In contrast, DNA-based mutation analysis in dried blood spots is used for the high-risk screening in the Canadian Oji-Cree Indians because they are at risk of being missed by MS/MS-based screening due to their extremely *low* excretor phenotype.[21]

Significant differences still exist in the diagnostic procedure, treatment and monitoring of affected patients so that there is a wide variation in the neurologic outcome of pre-symptomatically diagnosed patients.[40] At this time of rapid expansion of neonatal screening for GCDH deficiency worldwide, the major aim of this guideline is to examine the common practice and to formulate guidelines for diagnosis and management of this rare inborn error of metabolism based on the best evidence available. It should also provide comprehensive information on the nature of GCDH deficiency that can serve as the template for revisions in this rapidly evolving field. Undoubtedly, more work has to be done to increase the level of evidence in the diagnosis and management of this rare disease. For this purpose, a prospective follow-up study has been started in 2003 (www.metabnet.de).

The guideline is aimed at healthcare professionals involved in the diagnosis and management of children with GCDH deficiency. It also discusses issues often raised by families so it is hoped that they will find it useful.

1.2 DEFINITION AND DIFFERENTIAL DIAGNOSES

GCDH deficiency is defined as inherited deficiency of GCDH confirmed by enzyme analysis and/or mutation analysis. All other signs, symptoms and laboratory abnormalities that are found in affected patients are not pathognomonic and thus only that the diagnosis is suspected not confirmed. These include macrocephaly, acute encephalopathy, basal ganglia injury, leukoencephalopathy, movement disorders, subdural and retinal bleedings, and increased urinary excretion of glutaric and 3-hydroxyglutaric acids. All of these include a wide differential diagnosis, such as benign familiar macrocephaly, communicating hydrocephalus, other inborn errors of metabolism causing macrocephaly (eg Canavan's disease and other organic acidemias, mucopolysaccharidosis), hepatic or uremic encephalopathy, Reye or Reye-like syndrome encephalitis/meninigitis, metabolic stroke in primary mitochondrial disorders, classical organic acidurias (methylmalonic and propionic acidurias) and urea cycle defects (eg ornithine transcarbamylase deficiency), intoxications (eg 3-nitropropionic acid), asphyxia, HIV encephalopathy, infectious or post-infectious striatal necrosis (eg *Mycoplasma pneumoniae*), leukodystrophy, infantile cerebral palsy, battered child syndrome, multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II), glutaryl-CoA oxidase deficiency (glutaric aciduria type III), ketosis, short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, pseudo-glutarylcarnitinemia (in medium-chain acyl-CoA dehydrogenase deficiency).

☑ The correct classification of GCDH deficiency has important practical implications when devising individual treatment plans and giving appropriate information to children and families and thus diagnostic work-up should be performed by metabolic specialists.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Stardards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guidline recommendations will not ensure the correct diagnosis and satisfactory outcome in every case, nor

should they construed as including all proper method of diagnostic work-up and care or excluding other acceptable methods aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. The judgement should only be arrived at following discussions of the options with the patient and his family, covering the diagnostic and treatment choices available. However, it is advised that significant departures from the guideline should be fully documented in patient's case notes at the time the relevant decision is taken.

1.4 REVIEW AND UPDATING

This guideline was issued in 2006 and will be considered for review in three years.

2 Neonatal, high-risk and selective screening, and confirmation of diagnosis

2.1. Neonatal and high-risk screening

2.1.1 Major aims

Timely diagnosis and start of treatment, ie before an acute encephalopathic crisis, is likely to result in a better outcome than diagnosis and start of treatment after the onset of neurologic disease.[23,24,27-29] Therefore, neonatal and high-risk screening aim to reduce the *a priori risk* for an acute encephalopathic crisis and neurologic disease, and are a *conditio sine qua non* for a good outcome. | 2^+ 2^-

2.1.2 Definitions

MS/MS-based **neonatal screening** for GCDH deficiency is performed within the regular neonatal screening or in expanded neonatal screening programmes and includes patients with an standard *a priori* risk for GCDH deficiency. **High-risk screening** for GCDH deficiency is performed in neonates with an *a priori risk* for GCDH deficiency that is known to be elevated including patients from high-risk families (previously diagnosed index patient) or high-risk cohorts (high carrier frequency), and neonates antenatally diagnosed by amniocentesis or chorion villus biopsy. High-risk screening can be performed by MS/MS or alternative methods, eg mutation analysis in dried blood spots or organic acid analysis in urine.

2.1.3 Tandem mass spectrometry

Epidemiology

Summarizing results from international screening laboratories,[11,14,15,38] the prevalence of GCDH deficiency is approximately 1 in 100,000 newborns.[1] However the prevalence considerably varies in different countries and confidence intervals are still wide due to relatively small numbers of patients diagnosed by neonatal screening (**Annex 1**). Notably, the prevalence is lower than suggested before.[41] | 3 4

Tests

Neonatal screening for GCDH deficiency by MS/MS is performed in several laboratories all over the world (**Annex 1**).[1,11,12,15,16,37-39] The diagnostic test is glutarylcarnitine (C5DC) in dried blood spots (DBS). Some laboratories are also using ratios to other measured acylcarnitines in addition. | 3

Some laboratories repeat the analysis on another bloodspot from the same DBS as an internal quality but this is considered a matter that should be dealt with in individual laboratories and no recommendations are given in these guidelines.

Cut-off levels

A C5DC level above the cut-off value is considered a positive case. The cut-off level for C5DC has to be set independently in each laboratory as it will be influenced by many factors including the (internal) standard used, time of sampling of DBS, inter-laboratory variations etc (**Annex 1**). It will also be influenced by the acceptability of the number of false positives by the screening laboratory and in the society where the screening takes place. Cut-off levels are typically adjusted with more experience of screening. This is likely to continue. At present, there is no general recommendation for the establishment and setting of cut-off levels (see international discussions on methodology and ethics[42]).

Diagnostic pitfalls

Probably not all patients, however, can be diagnosed by this method, as there are patients with high residual enzyme activity and a normal or only slightly increased concentration of the diagnostic metabolite glutarylcarnitine (C5DC). Patients with GCDH deficiency missed by newborn screening[38,43] or by retrospective analysis of the newborn blood spots[44,45] have been reported. Patients were missed by neonatal screening because an initial positive screening result became normal in a repeat sample. To circumvent this problem most laboratories are now using additional tests for follow-up investigations of initially positive screening results (eg qualitative or quantitative determination of urinary glutaric and/or 3-hydroxyglutaric acids). | 3 4

Patients with a high residual GCDH activity with a low excreting phenotype are theoretically at higher risk of being missed by MS/MS-based neonatal screening in DBS (Greenberg, personal communication | 3 4

2004),[21,44] however, some patients with a high residual GCDH activity have been diagnosed by new born screening (B. Wilcken, personal communication 2004).[1]

Apparent increases in C5DC have been demonstrated in MCAD deficiency, most probably because of acylcarnitines of identical mass, such as hydroxyoctanoyl- and hydroxydecanoylcarnitines.[46] In patients with multiple acyl-CoA dehydrogenase (MAD) deficiency, C5DC can also be elevated but in this condition an elevated C5DC is accompanied by an elevation of other acylcarnitines (e.g. C5, C8).[11,14] 3

☑ For neonatal screening for GCDH deficiency MS/MS should be used to detect C5DC in DBS.

2.1.4 Alternative methods

Clusters of affected patients from genetic isolates with high carrier frequencies (up to 1 in 10 newborns) were identified in the Amish population,[29,31] the Oji-Cree Indians[21,22] and the Irish travellers.[27,28] The Amish and Irish Travellers have a high excretor phenotype, whereas the Oji-Cree are low excretors. High-risk screening in the Amish and the Irish travellers was first performed by organic acid analysis but has been shifted to the detection of C5DC in DBS. There have been no documented false negatives in the Amish population and the Irish travellers. In contrast, high-risk screening in the Oji-Cree population by MS/MS produced a high number of false negatives (Greenberg, personal communication) and, recently, a DNA-based high-risk screening in DBS has been implemented.[21] 2^- 3 4

☑ In a cohort of low excretors with a high carrier frequency and a known *GCDH* gene mutation, neonatal high-risk screening by MS/MS may produce a false negative result. Screening of these cohorts should consider alternative methods, such as DNA-based screening in DBS.

2.1.5 Confirmation of a positive screening result

A C5DC concentration above the current cut-off level is generally considered to indicate an affected patient, although the diagnosis has not yet been confirmed. A positive screening result should be confirmed by alternative techniques to MS/MS, including determination of GA and 3-OH-GA in urine by GC/MS (with stable isotope dilution assay),[10] mutation analysis in the *GCDH* gene[5,8,9] and GCDH enzyme analysis in isolated peripheral leukocytes or cultured fibroblasts.[3]

If the characteristic pattern of urinary GA and 3-OH-GA is not found, the concentration of 3-OH-GA should be determined by a sensitive stable isotope dilution method. A normal 3-OH-GA excretion will exclude the diagnosis (=*false positive*). An elevated urinary excretion of 3-OH-GA should be followed by mutation analysis and start of treatment. The finding of two known disease-causing mutations will establish the diagnosis. The presence of only one known disease-causing mutation or no mutations should lead to the determination of GCDH activity. Low enzyme activity will again establish the diagnosis of GCDH deficiency while a normal activity will exclude the diagnosis (=*false positive*).

Figure 1 shows a flow sheet depicting the neonatal and high-risk screening, and the confirmatory diagnostic procedure following a positive screening result.

☑ For the confirmation of a positive neonatal screening result, a specific diagnostic work-up is required, including a quantitative analysis of glutaric and 3-hydroxyglutaric acids in urine, mutation analysis, and enzyme analysis.

2.2. Selective screening

2.2.1 Pretest probability

If neonatal or high-risk screening programmes are not established, the diagnosis of GCDH deficiency should be made by selective screening in metabolic centers or specialized metabolic laboratories. The major disadvantages of this approach, however, is that there is no single pathognomonic sign or symptom in GCDH deficiency that is useful to safely detect GCDH deficiency before the manifestation of acute encephalopathic crises. In consequence, the majority of patients are diagnosed by selective screening when already neurologically symptomatic.[5,13,22-29,31] Only a small number of patients have been diagnosed before an acute crisis in the course of diagnostic work-up of macrocephaly. However, macrocephaly *per se*, although being frequent (75-80%) in affected patients, is non-specific and has a low pretest probability for GCDH deficiency. If combined with other clinical and neuroradiological signs, such as dystonia, subdural or retinal bleedings, frontotemporal atrophy, or bitemporal arachnoid cysts, the probability for GCDH deficiency increases. **Annex 2** includes a tool to estimate the pretest 2^+ 2^- 3

probability for GCDH deficiency, and **Annex 3** summarizes frequent neuroradiologic findings.

2.2.2 Methods

If there is clinical or neuroradiologic suspicion (**Annexes 2 and 3**), selective screening for GCDH deficiency should be initiated. In this section, we comment on the most frequently used methods and summarize best practice based on the clinical experience of the guideline development group.

Detection of C5DC by MS/MS in DBS and urine

As with to neonatal and high-risk screening, detection of C5DC in DBS is also useful for selective screening. It not only detects C5DC, but also decreased levels of free carnitine as a consequence of increased formation and urinary losses of C5DC. If so, a single oral loading with 100 mg/kg carnitine will increase the production of C5DC, which can be analyzed in blood and urine. Note that false negative results may be encountered in patients with a mild biochemical phenotype (low excretors) – even with carnitine loading. In contrast, C5DC concentrations in urine may be still elevated during secondary carnitine depletion (when blood glutarylcarnitine concentrations may decrease to normal values) and may be also helpful for the detection of low excretors.[17] 3

Quantitative analysis of glutaric and 3-hydroxyglutaric acids in urine by GC/MS

Affected patients will excrete varying amounts of glutaric acid, 3-hydroxyglutaric acid, and – inconsistently – glutaconic acid.[10] The majority of patients are high excretors.[5,13,23,24,26,29] Each laboratory should establish its own reference values. Whereas glutaric acid is excreted in high amounts in *high excretors* (GA >100 mmol/mol creatinine), it may be absent or near normal in *low excretors* (GA <100 mmol/mol creatinine). The separation of 3-hydroxyglutaric acid from 2-hydroxyglutaric acid may be cumbersome. Mass selective detection (the mass spectra of 3-hydroxyglutaric and 2-hydroxyglutaric acids show distinct differences) should always be performed. The diagnostic relevance of glutaconic acid is limited. Since quantitative organic acid analysis has some advantages for selective screening compared to MS/MS in DBS, ie higher sensitivity and specificity particularly in patients with secondary carnitine depletion, this is usually the first line method for selective screening. 2^+ 2^- 3

False positive results have been observed for the following diseases and metabolic conditions.

Glutaric acid ↑	**3-Hydroxyglutaric acid ↑**
Intestinal disease	Severe ketosis
Severe ketosis	Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	
Methylmalonic and propionic acidurias	
Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II)	
Glutaryl-CoA oxidase deficiency (glutaric aciduria type III)	
2-Oxoadipic aciduria	
Primary defects of respiratory chain	

GCDH enzyme activity in fibroblasts or leukocytes

This is the 'gold standard' for confirming the diagnosis with a sensitivity of 100%.[3,7] GCDH deficiency varies considerably ranging from complete loss of GCDH activity in the majority of patients up to near heterozygous state, ie 30% residual activity.[7,24,44,45,47] 2^+ 3 4

Mutation analysis of the GCDH *gene*

More than 150 disease-causing mutations have been reported. The sensitivity of *GCDH* gene mutation analysis is 98-99%.[7-9,24] 2^+ 3

Loading tests

Loading tests using lysine or prolonged fasting tests provoking catabolism are usually not established with age-matched controls, potentially harmful and should not be used for selective screening.

Alternatively, safe loading tests can be performed *in vitro* using lymphoblasts or peripheral mononuclear blood cells,[48] however, there is no evidence that loading tests are necessary for the confirmation of diagnosis.

☑ If clinical, neuroradiological or biochemical signs or symptoms are present that increase the *a priori* risk for glutaryl-CoA dehydrogenase deficiency, a specific diagnostic work-up should include analysis of glutaric and 3-hydroxyglutaric acids in urine, *GCDH* gene mutation analysis, and enzyme analysis.

Figure 1 summarizes the diagnostic procedure for neonatal, high-risk and selective screening, and confirmation of diagnosis in GCDH deficiency.

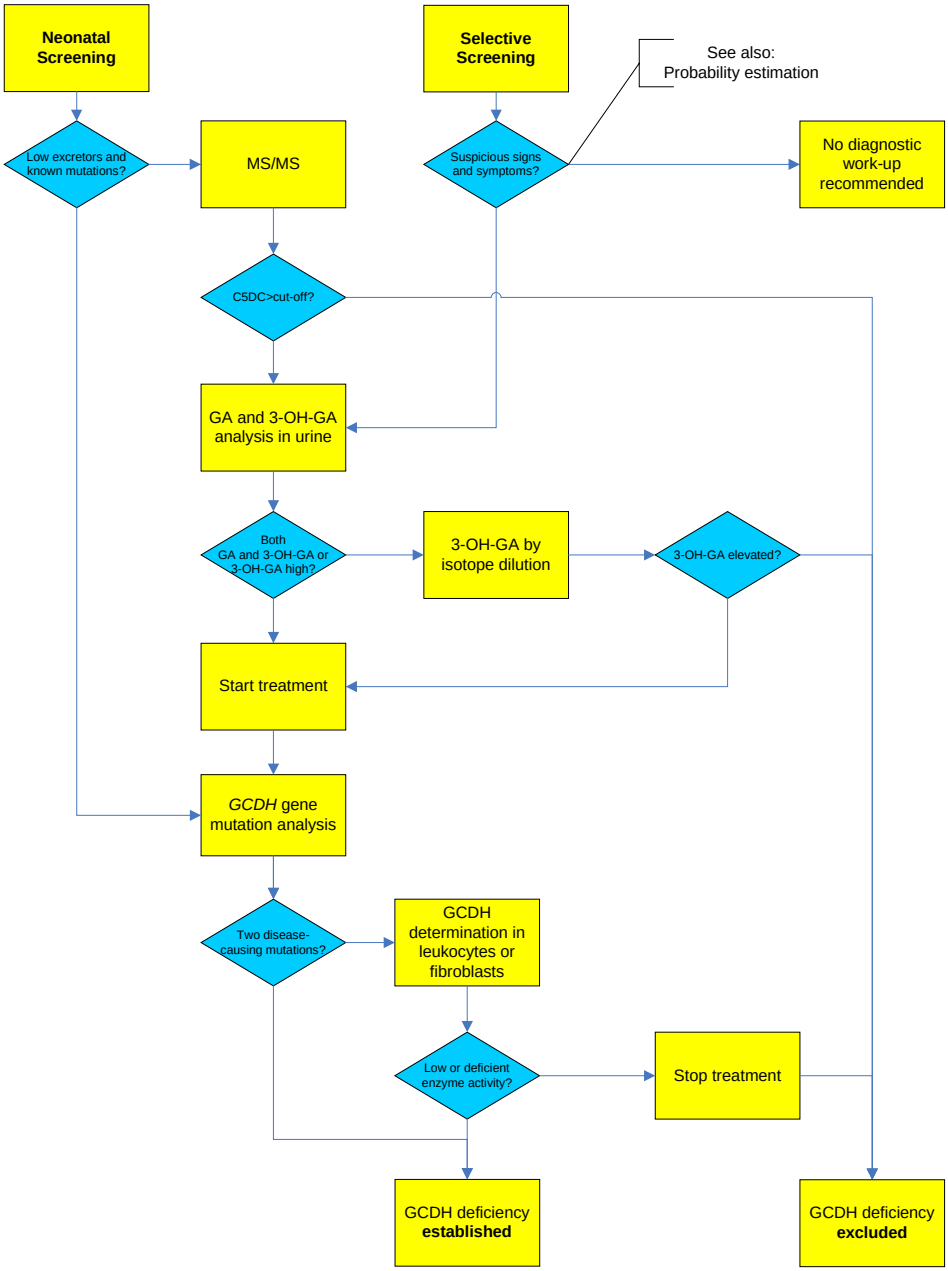
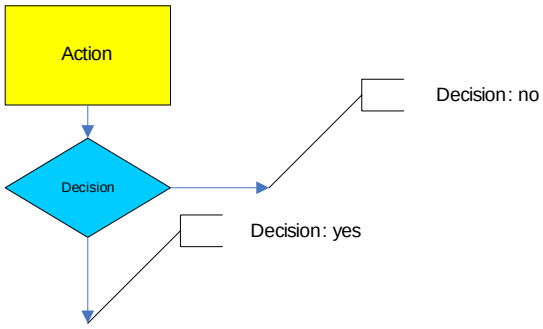


Figure 1. Neonatal and selective screening and confirmation of diagnosis
In general, neonatal and high-risk neonatal screening for GCDH deficiency is performed using MS/MS (start in the flow chart: "Neonatal screening"). For high-risk neonatal screening, a mechanism for the flagging of Guthrie cards of high-risk neonates should be established in screening laboratories. In low excretor cohorts with known mutations, neonatal screening should be performed using *GCDH* gene mutation analysis to avoid a considerable number of false negatives. Selective screening should be started if diagnosis of GCDH deficiency is suspected. To estimate the probability of GCDH deficiency see **Annex 2**.


Action
Decision
Decision: no
Decision: yes

3 Metabolic maintenance treatment

☑ The prescription of any dietary treatment or medication requires an assessment of risk and of benefit. It may be necessary to adjust the treatment to meet individual needs in case of weight loss, malnutrition, feeding problems or adverse effects of therapy. To sucessfully cope with these problems, dietary treatment and pharmacotherapy should be implemented by an interdisciplinary team including metabolic pediatricians, dieticians, nurses and occupational therapists. Parents and patients should have regular training including written information on dietary treatment to minimize the risk of dietary mistakes.

3.1 EFFECT OF TREATMENT ON OUTCOME

Whereas the outcome in GCDH deficiency is poor in patients who have been diagnosed **after** acute encephalopathic crises,[5,13,19,22-25,26,29,31] most patients remained clinically asymptomatic if diagnosed and treated **before** these crises.[23,24,27,28,29,36,49] Although some pre-symptomatically diagnosed patients have still developed neurological complications, the value of early diagnosis and treatment is undisputed (**Annexes 7** and **8**). Since dietary treatment is used in combination with carnitine, riboflavin, and emergency treatment in the majority of children, the relative efficacy of each single components is not known. However, a recent international cross-sectional study on 279 patients has demonstrated a beneficial effect for **lysine-restricted diet** and **carnitine supplementation** but not for protein-restricted diet or riboflavin (**Annex 7**).[24] 2+ 2− 3 4

The value of dietary treatment is unclear in patients who have been diagnosed and treated **after** encephalopathic crises but some patients may benefit by prevention of further encephalopathic crises or progression of neurological deteroriation. There may be even some mild neurological improvement (**Annex 8**).[13,19,23,26,29,50,51,52] In contrast, carnitine supplementation prevents secondary carnitine depletion and may partially improve or stop the progression of neurological disease, and reduces the mortality.[19,23,24,29,32,34,51,53]

3.2 MAJOR GOALS OF MAINTENANCE TREATMENT

A diet that meets the **general**, **age-dependent** and **individual requirements** for the daily intake of energy and essential nutrients, such as amino acids, minerals, and micronutrients, should form the basis of the dietary treatment to ensure normal growth and development. Specifically the aim in GCDH deficiency is to reduce the production of (toxic) organic acids by restricting the intake of lysine and tryptophan intake whilst maintaining adequate intake of all essential nutrients.

Pharmacotherapy in GCDH deficiency should stimulate detoxification of organic acids, prevent secondary carnitine depletion, and activate the deficient GCDH enzyme.

3.3 DIETARY TREATMENT

3.3.1 INTERNATIONAL DIETARY RECOMMENDATIONS

International dietary recommendations have been developed and successively optimized by different international organizations[54-61] outlining the age-dependent needs of the growing child (**Annex 4**). These recommendations also form the basis for dietary treatment in GCDH deficiency. 4

☑ Any alternative approach to dietary treatment in GCDH deficiency that does not fulfil the international dietary recommendations is not recommended and should be considered as potentially dangerous.

3.3.2 INDIVIDUALIZATION OF DIETARY TREATMENT

To make sure that the majority of children get a sufficient amount of nutrients, international dietary guidelines are usually set to be the mean plus two standard deviations. This means that most children can manage on less than generally recommended. Children with GCDH deficiency may have an increased requirement for nutrients and energy (e.g. due to increased musclar activity), an impaired intake (e.g. due to feeding problems), and/or increased losses (e.g. due to diarrhoea and sweating). However, loss of mobility decreases the energy demand.[52,62] It is unknown whether dietary recommendations will meet these possibly varying demands.[54-61] To achieve normal growth and development, dietary treatment needs an individualisation taking into account these guidelines. 4

3.3.3 LYSINE RESTRICTION VERSUS PROTEIN RESTRICTION

Glutaric and 3-hydroxylglutaric acids derive from lysine (Lys), hydroxylysine, and tryptophan (Trp). To reduce the production of these (toxic) organic acids, dietary treatments have been developed to reduce the intake of the relevant precursors, in particular Lys. At present, two strategies for the dietary treatment of GCDH deficiency exist, ie **Lys-restricted diet** and **protein-restricted diet**. The goal of both strategies is to reduce Lys intake via restriction of natural protein while maintaining a sufficient intake of essential nutrients and energy substrates.[52,54-61-63] The major difference between them is that Lys-restricted diet is calculated primarily via an estimation of daily Lys intake, whereas protein-restricted diet is based on calculation of natural protein. To achieve an optimal reduction of Lys, it is necessary to understand that the Lys content varies in different natural proteins (**Annexes 4 and 5**). Animal foods such as meat, fish, egg, and milk are rich in Lys and need to be restricted to a greater extent than cereals, vegetables and fruits which are much lower in Lys content. Lys-free amino acid (AA) mixtures should be supplemented in patients receiving a Lys-restricted diet to reduce the risk of malnutrition (**Annex 6**). 4

Lys- and protein-restricted diets have been used for more than 10 years worldwide. Although both of these have been used, we will focus on Lys-restricted diet for the following reasons:

Basic principle: An estimation of daily Lys intake can be achieved more exactly using a calculation of Lys instead of protein (**Annexes 4 and 5**).

Outcome: The frequency of acute encephalopathic crises is lower in pre-symptomatically diagnosed patients treated with Lys-restricted than with protein-restricted diet (**Annexes 7 and 8**).[21,23,24,27-29] 2^+ 2^- 3

C **Lysine-restricted dietary treatment (ie restriction of Lys to minimum requirements *plus* supplementation of Lys-free AA mixtures) is recommended for the metabolic maintenance treatment of GCDH deficiency, in particular in pre-symptomatically diagnosed patients up to age 6 years.**

3.3.4 LYSINE RESTRICTION VERSUS TRYPTOPHAN RESTRICTION

Lys has become the major target for dietary treatment because of the following reasons: **1.** Natural protein consists of 2 to 9% Lys (**Annex 5**) but contains only 0.6 to 2% Trp, and thus Lys is the major source for these (toxic) organic acids. **2.** At present, accurate determination of Trp as it is protein bound is often not available in metabolic laboratories and, therefore, is often not easily and reproducibly incorporated in the follow-up of patients. **3.** Restriction of Trp intake can induce neurologic dysfunction (due to reduced production of serotonin), such as insomnia, irritability, depression and disturbance of temperature regulation, and pellagra (due to reduced production of nicotinic acid).

Trp depletion was thought to be associated with the death of one child treated with Lys- and Trp-free AA mixtures,[13] however, there is no definite proof for a causal link (although theoretically there was considerable evidence). Furthermore, no severe side effects have been reported in other children treated with Lys- and Trp-free AA mixtures in this disease but they may not have been recognized and reported. 3

3.3.5 AMINO ACID MIXTURES

The use of Lys-free AA mixtures, containing all essential AA (except for Lys) and usually (but not always!) minerals and micronutrients, are an integral part of the management of dietary treatment in GCDH deficiency. Following the manifestation of acute encephalopathic crises, a high frequency of feeding and gastrointestinal problems are found, including problems with chewing and swallowing, vomiting, gastroesophageal reflux, and diarrhea.[5,19,22-24,26-29,31,52,63] Taste and acidity of AA mixtures may add to previous gastrointestinal problems and a stepwise increase in AA mixtures may be necessary to prevent an aggravation of these problems. 2^+ 2^- 3 4

☑ Lys-free amino acid mixtures, preferably reduced in Trp and supplemented with essential nutrients and minerals, should be used for dietary treatment.

3.3.6 HOW TO AVOID MALNUTRITION

Lys restriction concomitantly decreases the intake of other essential nutrients which implies a 4

theoretical risk for malnutrition. The age-dependent demands change considerably during growth and development, in particular during the first years of life and teenage growth spurt.[54-62] Examples of dietary treatment in different age groups are given in **Annex 6**.

3.3.7 DIETARY TREATMENT AFTER AGE 6 YEARS

The long-term outcome in patients with GCDH deficiency is not well documented. Besides the onset of an acute encephalopathic crisis there is also evidence for chronic neurologic deterioriation in untreated patients: 1. *Late-onset* disease in adolescence or adulthood presentingwith leukoencephalopathy;[32-35] 2. *Insidious-onset* type in a subgroup of patients presenting with (progressive) neurologic disease in the absence of definite encephalopathic crises.[5,21,23,24,47] 2^+ 2^- 3

Since the benefit of dietary treatment after age 6 years has not yet been precisely evaluated but single case reports have suggested a potential benefit, it may be advisable to continue dietary treatment but using a less strict protocol than before age 6 years.

☑
- Avoid excessive intake of natural protein;
- Natural protein with a low Lys content should be preferred;
- Addition of essential nutrients should be considered, particularly if there are feeding problems.

3.3.8 CHILDREN WITH FEEDING PROBLEMS

Following acute encephalopathic crises, many children suffer from feeding problems due to impaired chewing and swallowing, and increased energy demand due to increased muscular tone.[5,13,19,22-24,26,28,29,31] These children are at increased risk for malnutrition if dietary management does not consider these changes.[52,62] In general, mobility and feedings skills are important prognostic parameters.[24] 2^+ 2^- 3 4

Although the individual approach to cope with these feedings problems may differ, there are some general recommendations that are helpful to consider.

☑
1. General recommendations
- Monitor growth and intake of essential nutrients.
- Keep the head in the midline position in dystonic patients to allow maximal mobility.
- Consider tube and overnight feeding.

2. Children with mild to moderate feeding problems
- Use semi-solid food (based on cereals, potatoes, milk, soy, vegetables, fruit), enrich food with protein-free formula powder (is already added with micronutrients) or use maltodextrin, cream and/or vegetable oil. Alternatively, protein-free high energy drinks can be administered as nutritional supplements.
- Increase the frequency and reduce the quantity of single meals.

3. Children with severe feedings problems
- Intensify the management (see 2).
- Reduce the volume of solid food (by increasing the concentration), concomitantly increase the quantity of fluids (preferably protein-free high-energy fluids). Solid food and fluids should be served separately.
- Implement a late meal.

4. Children with severe vomiting
- (See 2).
- Consider pharmacotherapy.
- Consider fundoplication or jejunostomy.

3.3.9 TRAINING

Apart from exact calculation of dietary treatment as outlined above, efficacy of dietary treatment critically depends on adequate information and education of parents and patients. Therefore, training and sufficient information of dieticians, parents and children is essential.

3.4 PHARMACOTHERAPY

3.4.1 L-CARNITINE

Concentrations of total carnitine and free L-carnitine in plasma or serum are significantly below normal in the majority of untreated patients.[23,29,36,49,53,64] Dietary treatment inevitably leads to a reduction of the intake of diet-derived L-carnitine. Although the body is capable of synthesizing L-carnitine, this is usually not sufficient to maintain a normal plasma concentration of L-carnitine. Conjugation of glutaryl-CoA is considered a physiologic detoxification to form non-toxic glutarylcarnitine and to replenish the intracellular CoA pool.[53,63,65] L-carnitine supplementation is thought to improve the outcome in the majority of patients with GCDH deficiency (**Annex 7**).[23,26,27,28,29,36,49,64,66] However, no randomized controlled studies are available to confirm the benefit of L-carnitine supplementation,[67] and no study has investigated the intracellular carnitine concentrations in patients with GCDH deficiency.

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C **L-Carnitine should be supplemented in all patients with GCDH deficiency and should be continued lifelong.**

☑ To prevent or reverse secondary carnitine depletion, an initial dosage of 100 mg L-carnitine/kg/d p.o. should be used and then should be adjusted to the concentration of free L-carnitine in plasma which should be kept in the normal range. Usually, carnitine supplementation can be reduced to 50 mg/kg/d p.o. in children (>6 years). A reduction of L-carnitine should be considered carefully if side effects, such as diarrhea and fish odour smell, occur.

No severe adverse events (e.g. sudden deaths or arrhythmias, such as in long-chain fatty acid oxidation defects) have been reported for L-carnitine supplementation in GCDH deficiency.

3.4.2 RIBOFLAVIN

Although an improvement of biochemical parameters has been suggested in single patients,[51,64] there is no firm evidence that riboflavin improves the neurological outcome of this disease.[21,23,24,26,28] Furthermore, if at all present riboflavin responsiveness is considered a rare condition in GCDH deficiency.

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C **Riboflavin should be administered only if riboflavin responsiveness has been proven.**

3.4.3 NEUROPROTECTIVE AGENTS

There is no firm evidence that administration of other drugs, such as phenobarbitone, *N*-acetylcysteine, creatine monohydrate, topiramate, glutamate receptor antagonists and antioxidants are beneficial for these patients[21,25,26,29] although theoretically they may appear to be beneficial.[68-70] In contrast, some of these drugs have a high frequency of adverse effects. These drugs should be subject to controlled studies.

2–
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D **Drugs with unproven neuroprotective effect for GCDH deficiency (eg antiepileptic drugs, glutamate receptor antagonists, creatine monohydrate, antioxidants) should not be used for the maintenance treatment of affected patients.**

Table 1 summarizes recommended best practice on metabolic maintenance treatment in GCDH deficiency based on the clinical experience of the guideline development group.

Table 1. Metabolic maintenance treatment

Consider an individualisation of treatment if normal growth and development is not achieved.

Age		0–6 mo	7–12 mo	1–3 y	4–6 y	> 6y
Lys-restricted diet						
Lys	*mg/kg/d*	100†	90†	80-60†	60-50†	Avoid excessive intake of natural protein; intake of natural protein with a low Lys content according to 'safe' values.[57]
Trp	*mg/kg/d*	20†	17†	17-13†	13†	
Protein (natural)*	*g/kg/d*	1.4-1.3	1.5-1.3	1.4-1.3	1.3-1.1	
Protein (AA mixtures)	*g/kg/d*	1.3-0.8	1.0-0.8	0.8	0.8	
Protein (total)*	*g/kg/d*	2.7-2.1	2.5-2.1	2.2-2.1	2.1-1.9	
Energy**	*kcal/kg/d*	115-82	95-80	95-82	90-78	
Micronutrients**	*%*	≥ 100	≥ 100	≥ 100	≥ 100	> 100
Pharmacotherapy						
Carnitine	*mg/kg/d*	100	100	100	100-50	30-50

*Calculations for natural protein intake are based on the Lys content of natural proteins and are given with the understanding of an ***additional*** administration of Lys-free AA mixtures. If sole protein restriction is performed (ie ***without*** administration of Lys-free AA mixtures), intake of natural protein should be performed according to 'safe' values of international recommendations (Annex 4). The relatively high intake of total protein beyond infancy in Lys restriction is due to the large quantity of food with a low Lys/protein ratio, ie natural protein with *low* biological value.

**According to international dietary recommendations.[55,56,60] Energy demand may vary in different climatic zones.

†Lys and Trp recommendations according to the *1st European Workshop on GCDH Deficiency* (Heidelberg, 1993) and international dietary recommendations.[54,61] These figures are used in metabolic centers performing a Lys-restricted diet.

4 Emergency Treatment

4.1 ACUTE ENCEPHALOPATHIC CRISES

Acute encephalopathic crises usually occurs up to age 6 years in association with **acute febrile illness**, **surgery** and **immunisation**. Although metabolic maintenance treatment may reduce this risk, it is insufficient to protect against encephalopathic crises if not intensified by emergency treatment. **Vomiting** and **diarrhoea** should be regarded as particularly threatening, since they will precipitate a **catabolic state**. There is a continuum between the onset of an intercurrent illness and the first signs of the neurological complications and thus the onset of these is difficult to ascertain. Children quite often show progressive reduction of **consciousness**. Following this initial period of progressive clinical deterioration striatal damage and subsequent motor dysfunction usually have an abrupt or **stroke-like onset**. Encephalopathic crises may be accompanied by **seizures**.[5,13,19,22,23,26,27,28,29,31]

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2^-
3

A detailed description of acute encephalopathic crises is given in **Annex 9**.

4.2 BASIC PRINCIPLES OF EMERGENCY TREATMENT

No study has investigated the comparative efficacy of different emergency treatment strategies in GCDH deficiency, however, emergency treatment *per se* is considered essential to prevent encephalopathic crises during intercurrent illness.[23,27-29,40,65,71,72,73] Emergency treatment follows the basic treatment principles of metabolic diseases of the *intoxication type*.[74,75] The following principles form the basis of emergency treatment protocols worldwide.

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D

The following basic principles should be used for emergency treatment:

- **Reverse catabolic state by administration of high-energy fluids (plus insulin).**
- **Reduce organic acid production by transient reduction or omission of natural protein. Continue to give Lys-free AA mixtures if at all possible.**
- **Amplify physiologic detoxifying mechanisms by carnitine supplementation and alkalination of urine.**
- **Prevent secondary carnitine depletion by carnitine supplementation.**
- **Balance body fluids and pH state by rehydration and buffering.**

4.3 MANAGEMENT OF EMERGENCY TREATMENT

4.3.1 PREVENTIVE CARE

The causes of a delayed decision to start emergency treatment are variable. **Table 2** summarizes helpful strategies to prevent hazardous delays.

Table 2. Proposed strategies to avoid delayed start of emergency treatment

Topic	Proposed strategies to avoid delay
Education and training of parents	Parents should be informed in detail about the natural history and the particular risks of GCDH deficiency, in particular the manifestation and neurological sequels of an acute encephalopathic crisis. They should be instructed precisely about the management of maintenance and emergency treatment, and this knowledge should be reinforced during regular visits at a metabolic center.
Treatment protocols	Written protocols for maintenance and emergency treatment should be given to all who may be involved (parents, metabolic centers, local hospitals) and kept updated. Parents should also receive an **emergency card** (preferably laminated) summarizing the key information on GCDH deficiency and basic principles of treatment (see also: **Annex 10**). The telephone number of the responsible metabolic center/physician should be written on the protocol and the emergency card.
Storage	Parents should be advised to care for sufficient storage of nutrients and drugs required for maintenance treatment and emergency treatment at home.
Local hospital or pediatrician	The closest hospital/pediatrician should be clearly instructed if GCDH deficiency has been newly diagnosed in a child. Key information (including written treatment protocols) should be provided to the local hospital/pediatrician without delay and *before* inpatient emergency treatment might be necessary. Inpatient emergency treatment should be started immediately in the closest hospital if necessary and follows the supervision of the responsible metabolic center to be contacted without delay.
Holidays	Metabolic specialists/centers in the vicinity of the holiday resort should be informed in

	written form about the disease and the recent treatment *before* the start of the holidays. The emergency card and treatment protocols should be translated *before* the start of the holidarys if necessary.
Infectious diseases	During infectious disease the responsible metabolic center/metabolic specialists should be informed (by parents or local hospitals/pediatricians) without delay to allow supervision of the emergency management. Parents should be instructed to call their doctor and/or metabolic consultant as soon as a temperature of 38.5 °C is noted and an intercurrent illness is suspected either, an upper respiratory infection, gastrointestinal infection or if increased irritability develops.
Surgery	If a surgical intervention is planned, responsible metabolic centers/specialists should be informed *before* such interventions to discuss the specific risks of affected patients with surgeons and anaesthesiologists, to recommend a protocol for the postsurgical metabolic management and to allow supervision of this period. If possible, the postsurgical metabolic management should be performed in a metabolic center. In general, fasting should be avoided, glucose infusions applied, and carnitine dosage doubled.

4.3.2 START OF EMERGENCY TREATMENT

The possibility of an acute crisis should be suspected during **each infectious disease**, **immunisation**, or **surgical intervention** during the vulnerable period for acute encephalopathic crises (age 0-6 years). In particular, conditions accelerating catabolic state, such as repeated **vomiting** and **diarrhoea**, and the manifestation of severe **neurological symptoms** (hypotonia, irritability, rigor, dystonia, reduced consciousness) should be considered as **alarming** symptoms. With increasing age, and in particular after age 6 years, the risk of acute neurological insult appears to be much reduced. This may be in part increased resistance to catabolic state but also that there is a vulnerable period in these patients.[19,23,24,29] 2^{+} 2^{-}

C **Emergency treatment should start without delay and should be performed aggressively during febrile illness, surgery and immunisation within the vulnerable period for acute encephalopathic crises (up to age 6 years).**

Emergency treatment should aim to start before the onset of alarming neurological symptoms, such as hypotonia, irritability, rigor, dystonia, reduced consciousness. The decision to institute emergency treatment and admission to hospital should be made very freely with a low index of suspicion.

4.3.3 HOME AND OUTPATIENT EMERGENCY TREATMENT

If the temperature is less than 38.5 °C and the child is not vomiting, is tolerating his/her formulae and if there is no alteration in level of consciousness, a trial treatment period at home of up to 12 hours is recommended. During this time period patients should be reassessed every two hours regarding state of consciousness, fever, and food tolerance. If home/outpatient emergency treatment is successful and no concerning signs or symptoms occur during this period, natural protein shall be reintroduced stepwise during the next 24-48 h. **Table 3** summarizes recommended best practice based on the clinical experience of the guideline development group.

Table 3. Home/Outpatient emergency treatment

A. Maltodextran / Dextrose*			
Age	**Maltodextran / Dextrose**		**Volume/day**
Years	*%*	*kcal/100 ml p.o.*	*ml p.o.*
0-1	10	40	min. 150/kg BW
1-2	15	60	120/kg BW
2-6	20	80	1,200-1,500
> 6	Particularly in severe diseases, it may be helpful to continue emergency treatment in analogy to age 0-6 years which may be individually adapted.		
B. Protein intake			
Natural protein	Stop (if AA mixtures are administered) or reduce to 50% of maintenance therapy (if no AA mixtures are administered), then reintroduce and increase within 1-2 days.		
AA mixtures	If tolerated, AA mixtures should be administered according to maintenance therapy: 0.8-1.3 g/kg BW/day p.o. (See also: Table 1, Metabolic maintenance treatment)		
C. Pharmacotherapy			
L-Carnitine	Double carnitine intake: 200 mg/kg BW/day p.o. (if tolerated)		

Antipyretics**	If temperature > 38.5 °C (101 F), eg ibuprofen (10-15 mg/kg BW per dose, 3-4 doses daily)

AA, amino acids; *BW*, body weight.
*Maltodextran/dextrose solutions should be administered every 2 hours day and night. If neonates and infants already receive a specific dietary treatment, protein-free food (eg AA mixtures) can be continued but should be fortified by maltodextran. Patients should be re-assessed every 2 hours.
**Paracetamol administration may be dangerous during acute metabolic decompensation (risk for glutathione depletion).
All calculations for A and B should be based on the expected and *not* on the actual weight!

4.3.4 INPATIENT EMERGENCY TREATMENT

If the patient shows recurrent vomiting, spiking temperature or even warning neurological signs, home/outpatient therapy is inadequate and inpatient emergency treatment should be initiated immediately in a metabolic center or the closest hospital (preferably under the guidance of a metabolic center). At hospital the child should be seen immediately, assessed and treatment begun. **Table 4** summarizes recommended best practice based on the clinical experience of the guideline development group.

Table 4. Inpatient emergency treatment

A. Energy requirement				
Calories	Increase to min. 120% of age-dependent daily requirements			
120 % of dietary recommendations *,†**	0-6 mo	7-12 mo	1-3 y	4-6 y
(kcal/kg BW/day)	98-128	96-109	98-109	96-98
B. Intravenous infusions				
Glucose	15(-20) g/kg BW/day i.v.			
Lipids	Start with 1-2 g/kg BW/day i.v., if possible increase stepwise to 2-3 g/kg BW/day i.v.			
Electrolytes	Electrolytes should be kept in the upper normal range (intermittent tubulopathy can occur during crises)			
Insulin	If persistent hyperglycemia >150 mg/dl and/or glucosuria occurs, start with 0.05 IE insulin/kg/h i.v. and adjust the infusion rate according to serum glucose (cave! Increased intracellular uptake of potassium)			
L-Carnitine	100 (-200) mg/kg BW/day i.v.			
C. Protein intake				
Natural protein	Stop for max 24 (-48) hours, then reintroduce and increase stepwise until the amount of maintenance treatment within 3-4 days. If the child is on a low protein diet without AA mixture, increase protein within 1-2 days.			
AA mixtures (lysine-free)	If tolerated, AA mixtures should be administered orally or by nasogastric tube according to maintenance therapy: 0.8-1.3 g/kg BW/day p.o. (see: Table 1. Metabolic maintenance treatment).			
D. Pharmacotherapy				
Antipyretics§	If temperature > 38.5 °C, eg ibuprofen 10-15 mg/kg BW per dose p.o.			
Antibiotics	Purposeful and timely administration			
Antiemetics	If vomiting; ondansetron 0.1 mg/kg BW per dose i.v. (max. 3 doses daily)			
Diuretics	If diuresis is less than 3-4 ml/kg/day; furosemide 0.5-1.0 mg/kg per dose i.v. (3-4 doses per day; cave! Rebound and electrolyte loss)			
Bicarbonate	If acidosis; alkalination of urine also facilitates urinary excretion of organic acids			
Antiepileptics	If seizures; start with phenobarbital and/or phenytoin i.v.			
E. Monitoring				
Blood	Glucose, blood gases, electrolytes, calcium, phosphate, complete blood cell count, creatinine, urea nitrogen, C-reactive protein, amino acids‡, carnitine state, blood culture, amylase/lipase††, creatine kinase††.			
Urine	Ketone bodies, pH			
Vital signs	Heart rate, blood pressure, temperature, diuresis; Glasgow Coma Scale if reduced consciousness			

*Although there are no exact calorimetric data of energy demands during infectious disease in GCDH deficiency, the experience from many metabolic centers is that energy should be increased to at least 120% of daily requirements to prevent the development of an acute crisis in GCDH deficiency.[23,27-29,75] It was demonstrated by indirect calorimetry that resting energy expenditure increased at least 30-40% during acute decompensation in patients with inborn errors of propionate metabolism.[76,77]
**DRI recommendations[60]; †D-A-CH recommendations[55], §Paracetamol administration may be dangerous in acute metabolic decompensation (risk for glutathione depletion); ‡during the recovery phase; ††useful for monitoring in severe illness to detect pancreatitis (amylase/lipase) or rhabdomyolysis (creatine kinase).
All calculations for A and B should be based on the expected and *not* on the actual weight!

4.3.5 EMERGENCY TREATMENT AFTER AGE 6 YEARS

The long-term outcome in GCDH deficiency is uncertain and recent studies have highlighted *late-onset* neurologic disease in previously asymptomatic and untreated patients.[32-35] Although no encephalopathic crisis has been documented after age 6 years, it cannot be excluded that febrile illness, surgery and immunisation is completely harmless at this age group. Furthermore, deaths in previously handicapped children with GCDH deficiency frequently occur during hyperpyrexia and aspiration pneumonia.[13,21-23,24,26,29] Future observations are important to estimate the neurological vulnerability to these conditions more precisely.

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2^{-}
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☑ Emergency treatment in children after age 6 years should be considered at least during severe diseases. It should be performed similarly to that in the age group 0-6 years with individual adaptation.

5 Management of neurologic complications

The manifestation of neurologic disease is frequent, in particular in untreated patients.[5,19,22-29,31] The most frequent neurological complications in GCDH deficiency are:

- **Movement disorders and motor handicap** (up to 95% of patients after an acute encephalopathic crises);[5,19,22-29,31]
- **Epilepsy** (4-40% of patients);[21,24,26,28,29]
- **Subdural bleedings** (10-30% of patients);[20,23,28-30,78-82]
- **Bitemporal arachnoid cysts** (frequency and origin unknown).[80,83-85]

2^+
2^-
3

Whereas movement disorders usually manifest following acute encephalopathic crises, seizures and subdural bleedings have also been described in some children not suffering an encephalopathic crisis.[23,30,78,79,82] The occurrence of bitemporal arachnoid cysts is independent from encephalopathic crises.[80,83-85]

5.1 MANAGEMENT OF MOVEMENT DISORDERS

5.1.1 CLASSIFICATION AND CONSEQUENCES OF MOVEMENT DISORDERS

The characteristic neurological sequel of these encephalopathic crises is a bilateral striatal damage which spreads out from the dorsolateral aspects of the putamina in a ventromedial direction, variably including caudate nuclei and globi pallidi (see also: **Annex 9**).[20,23,24,25,26,29] This lesion induces the variable clinical picture of an *"extrapyramidal"* syndrome which includes focal, segmental, or generalized dystonia, orofacial dyskinesia, choreoathetotic movements, dysarthria, and a certain degree of spasticity superimposing on the extrapyramidal signs. Ataxia is found in some children with a mild affection, whereas tremor and myoclonia are only rarely found.[23,25,26,28,29,32,34] Different types of extrapyramidal movements may be present at the same time, with one type often dominating the clinical picture (ie dystonia over dyskinesia). Dystonia is mostly the dominant extrapyramidal symptom, often accompanied by spasticity. Secondary complications, such as feeding problem, recurrent aspiration, joint (sub-)luxations, and pain are frequently found in dystonic patients.[23-25,26,29] Despite severe motor handicap, the intellectual functions are often well preserved.[23,26,29]

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2^-
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5.1.2 MULTI-PROFESSIONAL SUPPORT

The following aspects should be considered in each patient with movement disorder:

- Daily physical therapy to prevent contractures and to alleviate pain.
- A simple but important prerequisite is the correct positioning of the head. It should be kept in the midline position, which allows the patient the maximum of mobility and minimizes dystonia.
- Special care is needed to avoid aspiration with feedings.
- Increased muscular tension and sweating increase the requirement for calories and water.
- Percutaneous gastrostomy often leads to a dramatic improvement of nutritional status, a marked relieve of psychological tension and care load in the families and even reduction of the dystonic-dyskinetic symptoms.[23,25,26,29,52,62]
- Since movement disorders often result in secondary complications of the musculo-skeletal system which can be very painful, it is important to consider sufficient analgetic treatment or surgical correction.

☑ In all patients with GCDH deficiency, expert neurological evaluation should be performed by a neuropediatrician and/or later on by a neurologist to identify clearly the kind of movement disorder. In addition, dietitians, physicotherapists, occupational therapists, orthopediatrics, seeting and speech specialists, and providers of communication aids, should be consulted to enable multi-professional support for children with movement disorders.

5.1.3 DRUG THERAPY

Movement disorders in GCDH deficiency are difficult to treat and even experts cannot predict the efficacy of drugs due to a low level of evidence in clinical studies. The following drugs and neurosurgical interventions have been used for the treatment of movement disorders in GCDH deficiency:

Baclofen

Baclofen, a $GABA_B$ autoreceptor agonist, is generally used for symptomatic treatment of spasticity. Baclofen is often used in the long-term treatment of dystonia in GCDH deficiency. Together with diazepam it is the most widely used and efficacious drug in GCDH deficiency.[23,25,26,49,63] Oral baclofen should be used in dosages according to general recommendations. Intrathecal baclofen administration has been used with success in two children with severe dystonia.[26] | 2⁻ 3 4

Benzodiazepines

Diazepam and clonazepam have been successfully used in treating dystonia with positive results.[23,25,26,49,63] Dosages should be administered according to general recommendations. In some patients suffering from a high variability of severity of symptoms they can be adjusted daily within a given range. Intermittent treatment may be required to prevent tachyphylaxis. | 2⁻ 3 4

D **The benefit of affected patients from pharmacotherapy is uncertain. Baclofen and diazepam as monotherapy or in combination should be used as first line drug treatment for focal and generalized dystonia. Intrathecal baclofen should be considered as additional therapy for severe dystonia and spasticity.**

Anticholinergic drugs

Trihexyphenidyl is effective in treating dystonic symptoms. High doses of the drug can be reached only if trihexyphenidyl is increased slowly (starting with 1 mg/kg twice a day).[86] Adverse effects such as blurred vision and dry mouth are temporary. Memory deficit and confusion usually persist and require a reduction of the dosage. Adverse effects are encountered more frequently in adults than in children. | 4

D **Trihexyphenidyl should be considered as second line treatment for dystonia, in particular in adolescents and adults.**

Botulinum toxin

Botulinum toxin type A (BT-A) has been recently reported as an alternative therapy for focal dystonia in a girl with glutaric aciduria type 1.[86] Further nine patients (age 7 to 21 years) with focal dystonia or dystonia with superimposing spasticity have been successfully treated with BT-A (S. Kölker, personal communication). BT-A therapy is not or only partially efficacious if starting after the manifestation of significant joint contractures. BT-A should be administered by a neurophysiologist or neurologist well-experienced in this treatment. Some patients can develop immunity against the toxin, precluding further therapy; therefore, BT-A is usually administered every three months to minimize the formation of antibodies against the toxin. | 4

D **Botulinum toxin A should be considered as additional therapy for severe focal dystonia.**

Drugs with no proven or adverse effects

Some antiepileptic drugs (eg vigabatrine, carbamazepine, valproic acid) have been used for therapy of movement disorders in GCDH deficiency. **Vigabatrine** and **valproate** have been more commonly used in the past but showed little to no effect.[23,25,26,52] Nevertheless, a number of patients still continue on vigabatrine, which in view of the severe side effects should be carefully re-evaluated individually.

Carbamazepine was always unequivocally ineffective. Valproic acid effectively competes with glutaric acid for esterification with L-carnitine and may promote disturbances in the mitochondrial acetyl-CoA/CoA ratio.[23,52] | 2⁻ 3 4

L-DOPA did not show any improvement of the extrapyramidal syndrome.[25,26,49] In some patients, **amantadine** was used, however, failed to improve dystonic movement disorders (G. F. Hoffmann, personal communication).

D **Antiepileptics, L-DOPA and amantadine should not be used for the therapy of movement disorders in GCDH deficiency.**

5.1.4 NEUROSURGERY

Stereotactic surgery (pallidotomy) for severe generalized dystonia has been reported for 3 patients.[29,87] The results reported in two patients were unsatisfactory[29], whereas short-term improvement in dystonic | 3

symptoms were described in the other patient.[87]

D **The long-term benefit of dystonic patients from pallidotomy is uncertain. Pallidotomy should only be considered as part of a research project, not routine therapy.**

5.2 ANTIEPILEPTIC THERAPY

The frequency of seizures is increased in GCDH deficiency following acute encephalopathic crises, although a considerable variability exists in different cohorts.[21,23,24,26,29] Dystonic movements may be mistaken as seizures. Seizures are particularly frequent during the acute phase of encephalopathic crises and often do not continue later on. 2⁻3

5.2.1 DIAGNOSIS

☑ Diagnosis, choice of antiepileptic drug therapy and management of seizures in GCDH deficiency should follow existing guidelines (eg **SIGN guideline # 81: Diagnosis and management of epilepsies in children and young people**). Since the confirmation and classification of epilepsies has important practicable implications, the diagnosis of epilepsy and choice of antiepileptic drugs should be made by a pediatric neurologist or pediatrician with expertise in childhood epilepsy.

5.2.2 ANTIEPILEPTIC DRUG THERAPY

No study has investigated the comparative efficacy of antiepileptic drugs in GCDH deficiency. However, phenobarbitone, phenytoin, carbamazepine, topiramate and lamotrigine have all been used.

☑ Valproate should be avoided for antiepileptic drug therapy since it may enhance mitochondrial dysfunction and carnitine depletion.

5.3 SUBDURAL BLEEDINGS AND ARACHNOID CYSTS

5.3.1 DIAGNOSIS

Subdural bleedings may occur at any ages in GCDH deficiency but peaks during the time period of maximal extent of macrocephaly, ie infancy. Minor head traumas and disruption of elongated bridging veins have been suggested as underlying mechanisms. The exact frequency of subdural bleedings is unknown, since affected patients may remain neurologically asymptomatic and often do not develop suggestive clinical signs of increased intracranial pressure, such as vomiting, decreased consciousness, seizures or ataxia. Frequency of subdural bleedings has been estimated to 10-30% of patients according to neuroradiologic investigations.[20,23,26,29,30,78-80,82] Subdural bleedings in GCDH deficiency or other inborn errors of metabolism (eg Menkes disease) may be mistaken with shaken baby syndrome et vice versa.[78,81,88,89] Bitemporal arachnoid cysts have been described in some affected patients and have a high suspicion for GCDH deficiency, whereas unilateral arachnoid cysts are a rare occasion in this disease. Frequency and origin of these cysts are not yet known.[29,80,83-85] 2⁻3

D **Children with subdural bleeding and/or bitemporal arachnoid cysts should be investigated for GCDH deficiency, in particular if occuring in combination with macrocephaly and/or movement disorders.**

D **GCDH dehydrogenase deficiency should be excluded in children with suspected shaken baby syndrome.**

5.3.2 NEUROSURGERY

Neurosurgical interventions, such as fenestration, marsupialization, and ventriculo- or cystaperitoneal shunts, have been performed in a small number of affected patients with arachoid cysts and subdural bleedings. The majority of these patients had a poor neurological outcome or showed no significant neurological improvement. In particular, in undiagnosed patients who do not receive specific metabolic treatment neurosurgical interventions can precipitate an encephalopathic crisis.[80,82-84] Subdural bleedings may regress without neurosurgical intervention if metabolic treatment is intensified (E. Naughten, personal communication). 3 4

D **Neurosurgical interventions of arachnoid cysts and subdural bleedings in affected patients should be decided very cautiously and should be limited to acute life-threatening**

complications of increased intracranial pressure or of a midline shifting.

☑ The metabolic management during and after surgical interventions should be supervised by a metabolic specialist to decrease the risk of acute encephalopathic crises.

6 Monitoring therapy

6.1 MAJOR COMPLICATIONS OF GCDH DEFICIENCY

GCDH deficiency may be complicated by the manifestation of **acute encephalopathic crises**,[5,13,19,21-29,31] **subdural bleedings**,[19,20,23,26,29,30,79,80,82] or **malnutrition**.[23,62,90] Whereas encephalopathic crises manifest acutely, subdural bleedings and malnutrition develop insidiously. 2^+ 2^- 3 4

6.2 INVESTIGATIVE PROCEDURES

6.2.1 GENERAL AIMS

Regular therapy monitoring aims at evaluating relevant parameters that allow an estimation of the benefit and relevant side effects of a therapy (**risks and benefits**), therapeutic efficacy (**outcome**), and its adequate or inadequate performance (**compliance/non-compliance, mistakes**). In children, monitoring must also include an evaluation of psychomotor development, growth, and malformations. Therapy monitoring shall include those parameters that influence the decision on therapeutical interventions and has a **preventive aim**. Adverse changes should be detected at an early stage when they are still reversible. Potentially hazardous and invasive monitoring techniques should be used very cautiously. In addition, therapy monitoring shall be performed in a way that outcome can be analysed in a retrospective way, ie it shall also allow an evaluation of the outcome and the efficacy of a specific therapy.

In general, an optimal parameter for therapy monitoring shall have the following qualities: 1) No or low risk and inconvenience for the patient, 2) high validity, reliability, and objectivity, 3) high sensitivity and specificity, 4) high predictive value, 5) broad availability, 6) low cost.

☑ At present, there is no reliable marker that predicts the outcome of GCDH deficiency.

Since no study has evaluated the comparative efficacy and the predictive value of different theoretically relevant parameters, the guideline on therapy monitoring summarizes the best practice based on the clinical experience of the guideline developmental group and should serve as a guide for the mode and frequency of monitoring treatment.

6.2.2 CLINICAL MONITORING

Because of the insidious nature of acute metabolic decompensation in GCDH deficiency, clinical monitoring in this disease should be frequent and consists of different investigations, ranging from general pediatric parameters (eg anthropometry) to specific psychological tests. Expertise from general pediatricians, metabolic specialists, and dieticians from metabolic centers should be included into the evaluation of patients in an integrative way. In addition, consultations from other specialists (eg child neurologists, psychologists, physiotherapists, ophthalmologists) should be considered as necessary. This approach is recommended to assess the development in general, highlighting those parameters that reflect the risks of GCDH-deficient patients in particular, eg impaired motor function. In the following, a list of recommended investigations is summarized:

Development and growth

- Weight, height, head circumference, body mass index (use percentiles)
- Milestones of psychomotor development (internationally recommended scales)

Weight loss or insufficient gain of weight in affected children may herald impending metabolic decompensation and thus should be considered as a matter of concern. However, in patients with severe movement disorders gain of weight may remain poor despite intensive care and efforts.

Basic physical examination and history taking

- Standardized physical examination (see also: **Annex 11**)
- History taking

Neurological examination

- Standardized examination protocol (**Annex 11**)
- Video documentation

Psychological tests for the assessment of psychomotor development

- Standardized evaluation of motor, mental, speech and psychosocial development

In some countries, preventive care in infants, children, and adolescents follows a standardized schedule (eg "U1-9" and "J1-3" in Germany), including the above mentioned items – except for psychological tests. These preventive care protocols offer a reliable basis for a gross evaluation of general pediatric parameters but are insufficient for a detailed assessment of specific dysfunctions (eg delayed speech development).

☑ Therapy in diagnosed children with GCDH deficiency should be accompanied by regular professional monitoring which should be performed by a team of specialists. During the first year of life, clinical monitoring should be performed monthly (or at least bi-monthly), from age 1 to 6 years quarterly, and after age 6 years on a half-yearly (or at least yearly) basis. Monitoring should be re-inforced at any age if non-compliance, disease- or therapy-dependent complications have been newly detected.

6.2.3 ROUTINE BIOCHEMICAL MONITORING

The development of specific recommendations for biochemical monitoring of a metabolic disorder should be based on an understanding of the pathophysiology of the disease. For example: The monitoring of serum phenylalanine levels in patients with phenylketonuria; outcome is directly related to the blood level of the phenyalanine. Laboratory monitoring is essential to detect insufficient supply with essential amino acids, micronutrients and minerals before clinical manifestation of malnutrition.

At present, there is no reliable biochemical marker that is useful for the monitoring of maintenance treatment in GCDH deficiency, and there is still considerable variation in experts' opinion regarding the need for a biochemical monitoring of certain parameters.[66] 4

Organic acids

GA and 3-OH-GA have been suggested to contribute to neuronal damage in concert with additional maturational and environmental factors[68-70] and thus theoretically can be considered a candidate surrogate marker for GCDH deficiency. A decrease in the urinary concentrations of GA and 3-OH-GA have been demonstrated in patients (high excretors) following dietary treatment, whereas dietary treatment seems less effective at decreasing serum and CSF metabolite levels.[13,23,24,29,50] Furthermore, the biochemical response of dietary treatment cannot be detected by analysis of organic acids in the low excretor subgroup.[21,22] At present, there is no evidence that the metabolite levels in any of these specimens do correlate with the long-term clinical outcome. Specifically, low and high excretors share a similar risk for encephalopathic crises.[5,7,24] 2^+ 2^- 3

A dramatic decrease in CNS concentrations of GA and 3-OH-GA have been demonstrated in two *post mortem* studies in patients being effectively treated with a Lys-restricted diet prior to death,[50,91] whereas much higher CNS concentrations have been found in patients not receiving a specific diet.[34,92,93,94] This discrepancy between organic acids in body fluids and CNS tissue may be explained by hepatic and intracerebral *de novo* synthesis of GA and 3-OH-GA and the selective permeability of the blood-brain and blood-CSF barriers for dicarboxylic acids (such as GA and 3-OH-GA) which might be trapped in the CNS compartment.[70] Therefore, urine and plasma concentrations of GA and 3-OH-GA may just reflect the hepatic production of these dicarboxylic acids but do not give reliable information about the CNS concentrations which cannot be properly monitored. The currently available magnetic resonance spectroscopy systems lack sensitivity for the follow-up of cerebral GA and 3-OH-GA concentrations. 3

☑ Analysis of urinary excretion of GA and 3-OH-GA should be used to assess the primary biochemical response of patients (*high excretors*) to dietary treatment and to evaluate riboflavin sensitivity, however, should not be considered for regular long-term follow-up investigations.

Amino acids

Analysis of amino acids in plasma are useful to ensure that the overall patient nutrition is not being compromised, in particular during dietary treatment is performed and in children with feeding problems.[52,62] Trp should be assayed by specific HPLC analysis (or MS/MS analysis) as conventional amino acid analysis is not satisfactory. 3 4

D **Amino acids in plasma (fasting or at least 4 h postprandially) should be monitored during dietary treatment**

dietary treatment.

☑ Trp should be monitored by HPLC or MS/MS analysis, in particular in patients receiving Lys- and Trp-free amino acid mixtures and children with feeding problems who have a higher risk for Trp depletion.

Carnitine status

Carnitine supplementation prevents secondary depletion of free carnitine and improves the outcome in GCDH deficiency.[5,19,23,24,29,52,53] Analysis of carnitine status in plasma using HPLC or MS/MS analysis allows correct quantification of free carnitine and detection of carnitine depletion. Analysis of carnitine status gives valuable information on compliance. 2+ 2− 3 4

D **Carnitine status in plasma should be monitored to detect secondary carnitine depletion.**

Acylcarnitine profile

Assessment of C5DC and other acylcarnitines in dried blood spots can be performed using MS/MS analysis.[1,11,12,14,15,38] However, although this is a valuable tool for neonatal and high-screening, it has no impact for regular biochemical monitoring. C5DC will strongly increase upon the start of carnitine supplementation. 3 4

Additional biochemical monitoring

Regular analysis of other parameters, such as complete blood cell count, albumin, calcium and phosphate, and transaminases may be helpful for routine surveillance.[52] **Table 5** summarizes recommended best practice based on the clinical experience of the guideline development group on routine laboratory monitoring in GCDH deficiency. 3 4

Table 5. Routine laboratory monitoring in GCDH deficiency

		Frequency		
Parameter	**Rationale**	**0 – 12 mos**	**1 – 6 ys**	**> 6 ys**
Amino acids (plasma)	General nutritional status	Every 1-2 mos	Every 3 mos	Every 6 mos
Trp (plasma; HPLC)	Trp depletion	If Lys- and Trp-free AA mixtures are used and in children with feeding problems		
Carnitine (plasma or serum)	Avoid secondary depletion, check for compliance	Every 1-2 mos	Every 3 mos	Every 6 mos
Complete blood cell count	Routine surveillance, depletion of iron, folate, or cobalamin	Every 6 mos	Every 6 mos	Every 6 mos
Albumin	General nutritional status	If concerns exist about the nutritional status and in children with feeding problems		
Calcium, phosphate	Bone status, tubulopathy, check for compliance	Every 3 mos	Every 6 mos	Every 12 mos
Transaminases	Routine surveillance, metabolic decompensation	Every 3 mos	Every 6 mos	Every 12 mos

6.2.4 BIOCHEMICAL MONITORING DURING ACUTE ILLNESS

Vomiting, diarrhoea and reduced intake of nutrients and fluids increases the risk for dehydration, electrolyte loss, and acidosis, and subsequently acute encephalopathic crises.[5,13,19,22-24,26-29,31] Imbalances in the metabolic state, hydration and serum electrolytes, and complications should be detected on admission to adjust the emergency treatment. 2+ 2− 3

Table 6 summarizes recommended best practice based on the clinical experience of the guideline development group on routine laboratory monitoring in GCDH deficiency.

Table 6. Biochemical monitoring in GCDH deficiency during acute illness (on admission to hospital)

Parameter	Recommended in general	If clinically indicated
Complete blood count	+	
Sodium, potassium, calcium, phosphate	+	
Blood gases	+	
Glucose	+	

Ketone bodies	+	
Creatinine (serum), urea	+	
Carnitine status (plasma)	+	
C-reactive protein	+	
Transaminases	+	
Blood culture		**Bacterial infection, sepsis**
Amylase / lipase		**Pancreatitis**
Creatine kinase		**Sepsis, rhabdomyolysis**

6.2.5 NEURORADIOLOGICAL MONITORING

Cranial MRI and CT scans in affected patients often reveal a characteristic pattern of gray and white matter changes and abnormalities of CSF spaces that should prompt the diagnosis of GCDH deficiency (**Annex 3**). MRI scans, in particular those using diffusion-weighted images (EPI-SE) or apparent diffusion coefficient (ADC) maps, detect striatal lesions earlier and more reliably than CCT scans.[20,30,95-98] Some of these neuroradiological changes can also be detected by ultrasound,[99] even during the last trimester of pregnancy.[100] | 2⁻ 3

Indication

The above described neuroradiological findings are undoubtedly valuable to suspect GCDH deficiency in undiagnosed patients (**Annex 2**), however, neuroimaging using serial MRI or CCT scans is not considered essential for regular monitoring for three reasons: 1) The detection of neuroradiologic abnormalities that have no clinical correlate does not yet influence the clinical decision-making on metabolic maintenance treatment. 2) The risk-to-benefit ratio for neurosurgical interventions is poor. 3) Sedatives that are often required to obtain MRI and CCT scans in infants may have adverse effects.

☑ Neuroradiologic investigations should be performed in case of neurologic deteroriation. To reduce sedatives in newborns and infants, neuroradiological investigations should be performed within physiological sleeping times, most preferably after feeding.

Follow-up investigations on a yearly basis may be helpful after relaxation of metabolic maintenance treatment at school age to re-evaluate the indication of the recent treatment protocol (in particular if neuroradiologic abnormalities significantly progress). However, the benefit of serial investigations is unclear and, if performed, should be part of a research studies.

Methods

After clinical stabilization or improvement of patients who have developed neurological disease, minimal standard imaging protocol should include axial T1- and T2-weighted and sagittal T1-weighted images. A spin-echo T2-weighted (or double-echo) sequence with parameters adapted for the age of the child should be used to consider changing water contents of the developing infant brain. Water content is considerably higher in neonatal brain than in infants and decreases with age necessitating increased TR and TE to compensate for the longer relaxation times. Although the very short imaging time required for fast T2-weighted sequences makes these attractive, their contrast and sensitivity for changes in myelination are suboptimal and less than in spin-echo sequences. Fluid-attenuated inversion recovery (FLAIR) images in the axial plane are especially useful in detecting white matter disease and basal ganglia abnormalities. During acute encephalopathic crises, an EPI-SE MR image including ADC maps should also be obtained, since it detects acute neurological damage more precisely and earlier than conventional MRI techniques.[29,95-98] A proposal for a standardized MRI protocol is given in **Table 7**. | 2⁻ 3

If no MRI is available, neuroradiological investigation should be performed using CCT. As long as the fontanelle is open, cranial ultrasound can be used instead (but may miss hygromas) and can be performed without using sedatives. Additional MR methods, such as MR spectroscopy, are not yet indicated for clinical-decision making but may be part of research studies.[34,101-103] | 3

Table 7. MRI standard protocol (1.5 T)

SE, spin-echo; *FLAIR,* fluid-attenuated inversion recovery; *EPI-SE,* echo-planar imaging spin-echo; *TSE,* turbo-spin echo; *TR,* repetition time; *TE,* echo time; *ms,* milliseconds.

Sequence	Orientation	TR (ms)	TE (ms)
T1-SE	sagittal, axial	500-600	7-15
T2-SE or TSE	Axial	2500-3000	30-60, 70-120
FLAIR	Axial	Dependent on the age of the patient, sequence, inversion time and equipment	
EPI-SE	Axial		

7 Development of the guideline

7.1 THE GUIDELINE DEVELOPMENTAL GROUP

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7.2 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with **SIGN**[*] methodology. A systematic review of the literature was carried out using an explicit search strategy. Databases searched include Medline, Embase, the Cochrane Library, MedLink, AWMF and Orphanet. The year range covered was 1975-2005. Internet researches were carried out on various websites including international and national societies for inborn errors of metabolism (APS, ASIEM, Garrod Association, JSIEM, SIMD, SSIEM), and parent groups (Glutarazidurie e.V., IOGA). The main searches were selected and evaluated by a minimum of two members of the group using standard SIGN methodological checklist before conclusions were considered as evidence.

In parallel, the group performed an international cross-sectional study on GCDH deficiency enrolling 279 patients.[24] To further increase the level of evidence for important aspects of diagnosis and management in GCDH deficiency, a prospective follow-up study of newly diagnosed patients has been started in 2003 (further information: www.metabnet.de; Stefan.Koelker@med.uni-heidelberg.de). Its results will be an important basis for the revision of the guideline which is planned for 2009.

7.3 GUIDELINE DEVELOPMENT

The guidelines process was initiated following the *3rd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency* in Heidelberg, Germany (October 18-19, 2003). Three further meetings were held in Rimini, Italy (May 16-17, 2004), in Amsterdam, The Netherlands (August 30-31, 2004), and in Prague, Czech Republic (May 26-27, 2005).

7.4 SPECIALIST REVIEW

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7.5 FINANCIAL SUPPORT

Guideline development for GCDH deficiency was financially supported by the German Federal Ministry of Education and Science (BMBF # 01GM0305 to S. Kölker and G. F. Hoffmann), the Kindness for Kids Foundation, Munich, Germany (S. Kölker), and by Milupa Metabolics, Orphan Europe and SHS International.

Annex 1
Neonatal screening – Prevalence and cut-offs

Table A. Prevalence of GCDH-deficient patients diagnosed by neonatal screening in different areas of the world

Center (City, Country)	Author	Neonates screened (n)	Patient diagnosed (n)	Incidence
Pittsburg, Pennsylvania + neighbouring states, USA	Naylor and Chace (1999); Chace (2002)	1,020,000	13	1:78,500
Boston, New England, USA	Zytkovicz et al (2001) ; T. Zytkovicz (pers. commmun. 2004)	164,000	0	
Heidelberg, Baden Württemberg, Germany	Schulze et al (2003) ; Lindner et al (2004) ; M. Lindner (pers. commun. 2004)	605,000	6	1 :100,800
Munich, Bavaria, Germany	Roscher el al (2001) ; W. Röschinger (pers. commun. 2004)	540,000	6	1 :90,000
Sydney, NSW, Australia	Wiley et al (1999) ; Wilcken et al (2003) ; B. Wilcken (pers. commun. 2004)	550,000	4	1:137,500
Melbourne, Victoria, Australia	J. Pitt (pers. commun. 2004)	160,000	3	1:53,000
Copenhagen, Denmark	H. Simonsen (pers. commun. 2004)	120,000	0	
Overall incidence by newborn screening		**3,159,000**	**32**	**1:100,000***

*95% Confidence interval: 1:70,000-1:167,000

Table B. C5DC – Cut-offs and ratios

?, not reported

Center (City, Country)	Calculation method for C5DC cut-offs	C5DC cut-off levels (µmol/l)	C5DC ratios used if any
Pittsburg, Pennsylvania + neighbouring states, USA	?	?	C5DC/C16
Boston, New England, USA	8 SD above the mean	0.21	?
Heidelberg, Baden Württemberg, Germany	99.95th centile	0.17	C5DC/C8, C5DC/C16
Munich, Bavaria, Germany	4 SD above the mean	0.09	C5DC/C4, C5DC/C8, C5DC/C12
Sydney, NSW, Australia	99.95th centile	0.4	None
Melbourne, Victoria, Australia	?	?	None
Copenhagen, Denmark	12 SD above the mean	0.23	C5DC/C2, C5DC/C3

Annex 2
Selective screening – Probability estimation

The following table provides a tool to estimate the probability of GCDH deficiency. Nevertheless, it cannot be excluded that GCDH deficiency may present with an atypical clinical phenotype or unusual neuroradiological abnormalities. Furthermore, the probability for GCDH deficiency should be assumed to be high **1)** in undiagnosed children of known high-risk families or communities who present with any of the above mentioned clinical or neuroradiological signs and symptoms and **2)** if selective screening accidentally reveals elevated 3-hydroxyglutaric acid (in particular in the absence of ketosis or hypoglycemia), or elevated C5DC (in particular if medium-chain or multiple acyl-CoA dehydrogenase deficiency is excluded).

Probability estimation - 1			
A. Clinical presentation	**Low**	**Moderate**	**High**
	Macrocephaly Frontal bossing Delayed motor development Feeding problems	Reye-like syndrome (acute metabolic encephalopathy) Cerebral palsy (Intermittent) ataxia	Acute encephalopathy Dystonia (acute onset and/or progressive deteroriation) Orofacial dyskinesia
B. Neuroradiology	**Low**	**Moderate**	**High**
	Frontal atrophy or hypoplasia Subependymal pseudocysts Delayed myelination Dilated ventricles Dilated external CSF spaces Extrastriatal lesions (eg cerebellum, thalamus)	Subdural effusions Temporal atrophy or hypoplasia Leukoencephalopathy (adolescent, adult) Isolated pallidal lesion	Isolated lesion of putamen and / or caudate

Probability estimation - 2			
plus		**Neuroradiology**	
Clinical presentation	***Low***	***Moderate***	***High***
Low	**LOW**	**MODERATE**	**HIGH**
Moderate	**MODERATE**	**MODERATE**	**HIGH**
High	**HIGH**	**HIGH**	**HIGH**

Annex 3
Neuroradiologic findings in GCDH deficiency

The following table summarizes frequent neuroradiologic abnormalities as detected by cranial MRI scans, CCT scans, or ultrasound.

Cortex
Temporal hypoplasia / (fronto-)temporal atrophy
Basal ganglia and other nuclei
Signal changes / volume loss in the basal ganglia (putamen ≥ caudate > pallidum)
Lesions spread in the following direction starting from the dorsolateral aspects of the putamina: dorsal → ventral, lateral → medial
Facultory affection of extrastriatal nuclei (frequency is not known): eg thalamus, dentate nuclei
Cerebellum
Usually not affected
External CSF spaces
Widening of Sylvian fissure, subarachnoidal CSF spaces, and inter-hemispheric fissure
Subdural hematomas or hygromas
Bitemporal arachnoidal cysts
Internal CSF spaces
Ventriculomegaly
White matter
Delayed myelination
Signal changes in periventricular white matter (may also affect subcortical U fibres; this may be the prominent finding in *late-onset* type GCDH deficiency)
Reduced thickness of corpus callosum (agenesis is rare)
Subependymal pseudocysts (usually transient)

Annex 4
International dietary recommendations

A limitation of the use of international dietary recommendations as a basis of the dietary treatment in GCDH deficiency is that they refer to different **reference proteins**. In previous recommendations for age groups >6 months (ie when introducing weaning food), calculations of protein intake were based on natural protein from a mixed diet. In contrast, recent recommendations use a reference protein with a high **biological value** with a high degree of digestibility – continuously in all age groups. Because of the different reference proteins used the values for protein intake are *lower* in the recent than in the previous recommendations. Dietary treatment protocols using restriction of natural protein in general and animal products in particular – like in GCDH deficiency – have to consider these differences carefully. Since the biological value of natural protein used in these diets is much lower than in the reference protein, there is a risk for malnutrition if the calculation of dietary treatment is based on the recommendations based on a reference protein with a *high* biological value. Therefore, calculating a diet for GCDH deficiency using recent recommendations for dietary treatment must consider that these recommendations do not reflect the *lower* biological value of a diet based on natural proteins with a low Lys content.

Table 1. International recommendations for daily requirements of natural protein.
Protein requirements are given as g/kg body weight/day, except for *g/day. *AI*, adequate intake.

	Based on a reference protein with a *high* biological value					Based on a mixed diet	
	WHO 'safe' [54]	**Revised 'safe'** [57]	**DRI**[60]	**D-A-CH** [55]	**DRV (RNI)**[56]	**DGE**[58]	**RDA**[59]
Months							
0-1	-	2.69	1.52 (AI)	2.7	2.1	2.3	2.2
1-2	-	2.04	1.52 (AI)	2.0	2.1	2.3–2.1	2.2
2-3	-	1.53	1.52 (AI)	1.5	2.1	2.3–2.1	2.2
3-4	1.86	1.37	1.52 (AI)	1.5	2.1	2.3–2.1	2.2
4-5	1.86	1.25	1.52 (AI)	1.3	1.6	2.1–2.0	2.0
5-6	1.86	1.19	1.52 (AI)	1.3	1.6	2.1–2.0	2.0
6-9	1.65	1.09	1.5	1.1	1.5	2.1–2.0	2.0
9-12	1.48	1.02	1.5	1.1	1.5	2.1–2.0	2.0
Years							
1-1.5	1.26	1.0	1.1	1.0	1.1	1.7	1.8
1.5-2	1.17	0.94	1.1	1.0	1.1	1.7	1.8
2-3	1.13	0.92	1.1	1.0	1.1	1.7	1.8
3-4	1.09	0.9	1.1	1.0	1.1	1.7	1.8
4-5	1.06	0.88	0.95	0.9	1.1	1.6	1.5
5-6	1.02	0.86	0.95	0.9	1.1	1.6	1.5
6-7	1.01	0.86	0.95	0.9	1.1	1.6	1.5
7-8	1.01	0.86	0.95	0.9	28.3*	1.4	1.5
8-9	1.01	0.86	0.95	0.9	28.3*	1.4	1.2
9-10	0.99	0.86	0.95	0.9	28.3*	1.4	1.2
10-11	1.0	0.87	0.95	0.9	28.3*	1.1	1.0
11-12	0.98	0.86	0.95	0.9	42.1*	1.1	1.0
12-13	0.96–1.0	0.85	0.95	0.9	42.1*	1.1	1.0
13-14	0.94-0.97	0.84	0.95	0.9	42.1*	1.0	1.0
14-15	0.90–0.96	0.81	0.85	0.9	42.1*	1.0	1.0
15-16	0.87–0.92	0.81	0.85	0.8	45.4-55.2*	0.8–0.9	0.9
16-17	0.83–0.90	0.78	0.85	0.8	45.4-55.2*	0.8–0.9	0.9
17-18	0.80–0.86	0.77	0.85	0.8	45.4-55.2*	0.8–0.9	0.9
>18	-	-	0.8	0.8	-	0.8–0.9	0.9

Dietary treatment for GCDH deficiency should also include a well-balanced and sufficient supply with essential amino acids, minerals and micronutrients. Recommendations for essential amino acids are listed below.

Table 2. Recommended dietary allowance for amino acids at different ages[60]

Values are given as mg/kg body weight/day.
** *AI,* Adequate intake. Data are based on the average intake from breastfed infants.

Amino acid	0-6 months**	7–12 months	1–3 years	4-8 years	9-13 years	14-18 years
Histidine	23	32	21	16	17-15	15-14
Isoleucine	88	43	28	22	22-21	21-19
Leucine	156	93	63	49	49-47	47-44
Lysine	107	89	58	46	46-43	43-40
Methionine+cystine	59	43	28	22	22-21	21-19
Phenylalanine+tyrosine	135	84	54	41	41-38	38-35
Threonine	73	49	32	24	24-22	22-21
Tryptophan	28	13	8	6	6	6-5
Valine	87	58	37	28	28-27	27-24

Table 3. Estimates of amino acid requirements at different ages[54,61]

Values are given as mg/kg body weight/day. *?,* value is not specified.

Amino acid	Infants (3-4 months)	Children (2 years)	Children (10-12 years)	Adults
Histidine	28	?	?	12-8
Isoleucine	70	31	30-28	10
Leucine	161	73	45-42	14
Lysine	103	64	60-44	12
Methionine +cystine	58	27	27-22	13
Phenylalanine + tyrosine	125	69	27-22	14
Threonine	87	37	35-28	7
Tryptophan	17	12.5	4-3.3	3.5
Valine	93	38	33-25	10
Total essential amino acids (without histidine)	714	352	261-214	84

Annex 5
Estimation of lysine intake

Natural food

To achieve an optimal reduction of Lys intake, it is necessary to understand that the Lys content varies considerably in different natural proteins (ie 2-9% of natural protein).

Table 1. Average Lys content in protein from different kinds of food

Food	Lys content
	(% of total protein)
Fish	9
Meat and meat products	8
Breast milk	8
Cow milk, milk products	7
Eggs (whole)	6
Potatoes	6
Soy und soy products	6
Nuts	2–8.5
Vegetables	4–6.5
Fruit	2–6.5
Cereals and cereal products	2-4

Source: Bundesinstitut für Gesundheit, Verbraucherschutz und Veterinärmedizin (BGVV) (computerprogram). Berlin: Bundeslebensschlüssel (BLS) Version 4.5.

Therefore, Lys intake in affected patients cannot be simply estimated by intake of natural protein (like in phenylketonuria or maple syrup urine disease) but should refer to these differences. In general, animal products should be restricted, whereas cereals, vegetables, and fruits with a low Lys conten form the basis of dietary treatment in GCDH deficiency.

Table 2. Lys contents in different foodstuff (normalized to 5 g natural protein)

Quantity	Food	Protein	Lys
(g)		*(g)*	*(mg)*
40	Pasta without egg	5	95
65	White bread	5	100
240	Potatoes	5	290
250	Kohlrabi	5	210
165	Spinach	5	320
150	Cow milk	5	355
17	Salami	5	420

Source: Bundesinstitut für Gesundheit, Verbraucherschutz und Veterinärmedizin (BGVV) (computerprogram). Berlin:Bundeslebensschlüssel (BLS) Version 4.5.

Manufactured food

Lys content is usually not mentioned on the package of manufactured food or is even not known. However, information on the total protein content and a list of ingredients (often including the relative amounts of these ingredients) is usually given and broadly available. This information should be used to estimate the Lys content of manufactured food. Estimation of Lys content should be performed in analogy to dietary treatment in phenylketonuria and maple syrup urine disease using figures. However, in contrast to PKU and MSUD diets using only one fixed figure each, estimation of Lys for dietary treatment of GCDH deficiency should also refer to different Lys contents and, thus, different figures should be used according to the major source of natural protein in manufactured food.

Table 3. Estimation of Lys content in manufactured food

Manufactured food	Major source of protein	Lys content	Lys /protein
		(% of protein)	*(mg/g)*
Bread, noodles, semolina, flakes, cakes and cookies (without egg or milk)	Wheat, German wheat, corn, millet	3	**30**
Bread, noodles, semolina, flakes, cakes and cookies (without egg or milk)	Rye, oats, barley, rice	4	**40**
Fruit products, eg sorbet and juice	Fruit	4	**40**
Cereals, cakes and cookies (with egg and/or milk)	Wheat, German wheat, corn, millet, rye, oats, barley, rice, milk, egg	5	**50**
Ketchup, food relish soups and sauces (without meat, egg or milk)	Vegetables	5	**50**
Soy and potato products, soups and sauces (with meat, egg or milk)	Potatoes, soy, legumes, egg	6	**60**
Milk, cheese, joghurt and other dairy products	Milk	7	**70**
Meat products	Meat	8	**80**

Annex 6
Age-dependent problems of dietary treatment

This paragraph summarizes a recently published paper from Müller and Kölker (2004)[62] on dietary treatment in GCDH deficiency. The major aim of this publication was to highlight the age-dependent requirements and problems with dietary treatment in this disease in an exemplified way. Calculation models used aimed at simulating dietary treatment.

6.1 METHODS

Diets were calculated as follows: 1) General: All dietary protocols were in accordance with international dietary recommendations. [54-61] 2) Amino acid supplements: For the calculations, *Milupa GA 1* (age 0-1 year) and *Milupa GA 2 prima* (>1 year) mixtures were used which are free in Lys, low in Trp and are fortified with minerals, trace elements, and vitamins. 3) Sources of natural protein: Breast milk, infant formula, cow milk, cereals (wheat, rye), potatoes, vegetables, and fruits.

6.2 RESULTS

6.2.1 AGE 3 MONTHS (Fig. 1A)

During the first 6 months of age breast-feeding is a well-balanced nutrition for healthy neonates and infants. The protein content of breast milk is quite low but absorption is better than of infant formula. If intake of natural protein was limited to 1.5 g/kg body weight/day, supply with all essential AA was barely adequate and Lys intake was about 113 mg/kg BW (ie 106% of DRI recommendations[60]) in our calculation model. A further reduction of natural protein decreased the supply with essential nutrients below daily requirements. If Lys-free AA mixtures were added, the risk for malnutrition was decreased and intake of natural protein could be reduced to 1.3 g/kg BW/day.

In contrast, sole administration of infant formula diet, which contains a higher content of Lys, resulted in inadequate supply with essential AA if Lys intake was restricted to minimal requirements. To avoid malnutrition, supplementation with Lys-free AA mixtures was necessary, or – if not possible – intake of natural protein should be increased to 1.86 g/kg body weight/day (according to WHO "*Safe*").[54] Although the latter normalized the intake of essential AA, it also increased Lys intake to 142% of recommended intake (not shown). Intake of minerals and micronutrients was adequate using breast-feeding or infant formula without additional administration of Lys-free AA mixture or micronutrient mixtures – except for vitamin D.

6.2.2 AGE 9 MONTHS (Fig. 1B)

After implementation of additional protein sources to the diet (usually starting at age 5 months), the variance of Lys contents increases remarkably. In our calculation model, reduction of natural protein intake to 1.1 (-1.0) g/kg body weight/day resulted in inadequate supply with nearly all essential AA, minerals and micronutrients (in % of DRI recommendations[60]), such as calcium (34%), phosphate (39%), iron (53%), and vitamin D (36%) if natural protein with a low Lys content (and thus low biological value) was used.

Increasing natural protein intake to 1.3-1.5 g/kg body weight/day resulted in an adequate but scarce supply with essential AA (except for sulphur-containing AA). In contrast, this dietary protocol did not fulfil the requirements for minerals and micronutrients (% of DRI recommendations[60]), such as calcium (54%), phosphate (54%), and vitamin D (72%). Addition of Lys-free AA mixtures fortified with micronutrients or micronutrient mixtures lowered the risk for malnutrition at this age while keeping Lys intake constantly low.

6.2.3 AGE 3 AND 6 YEARS (Fig. 1C)

At age 3 years, a restriction of natural protein to 1.0 (-1.1) g/kg body weight/day resulted in a low Lys intake (76% of DRI recommendations[60]) and sulfur-containing AA (86%) in our model. Increasing natural protein to 1.3 (-1.5) g/kg body weight/day allowed a sufficient intake of essential AA while maintaining Lys at 102 (-129)% of recommended requirements. Requirements for minerals and micronutrients could not be fulfilled without additional supplementation. At 1.3 g protein/kg BW, the following minerals and micronutrients were below the recommended requirements (in % of DRI recommendations[60]): Calcium (39%), phosphate (58%), iron (52%), iodide (19%), vitamin B_1 (73%),

vitamin B_2 (72%), vitamin B_{12} (71%) and vitamin D (5%). If Lys-free AA mixtures (0.8 g/kg BW) fortified with minerals and micronutrients were added to this diet, all minerals and micronutrients (except for calcium [88%] and vitamin D [39%]) were above the recommended requirements. Alternatively, mineral and micronutrient mixtures could be used.

At age 6 years, the problems were the same. In brief, essential AA were adequately supplied at a daily intake of 1.3 (-1.5) g natural protein/kg body weight/day, whereas restriction to 0.9 g protein/kg BW resulted in low Lys intake (68 % of DRI recommendations[60]). Again, intake of minerals and micronutrients was not satisfactory.

6.2.4 CONCLUSIONS

The risk for malnutrition with essential AA and micronutrients varies among different age groups during the first 6 years of life. In parallel, the risk of failing at least one of the two major goals of dietary treatment in GCDH deficiency differs in these age groups. As outlined, the risk for malnutrition can be decreased by application of Lys-free AA mixtures (preferably fortified with minerals and micronutrients).

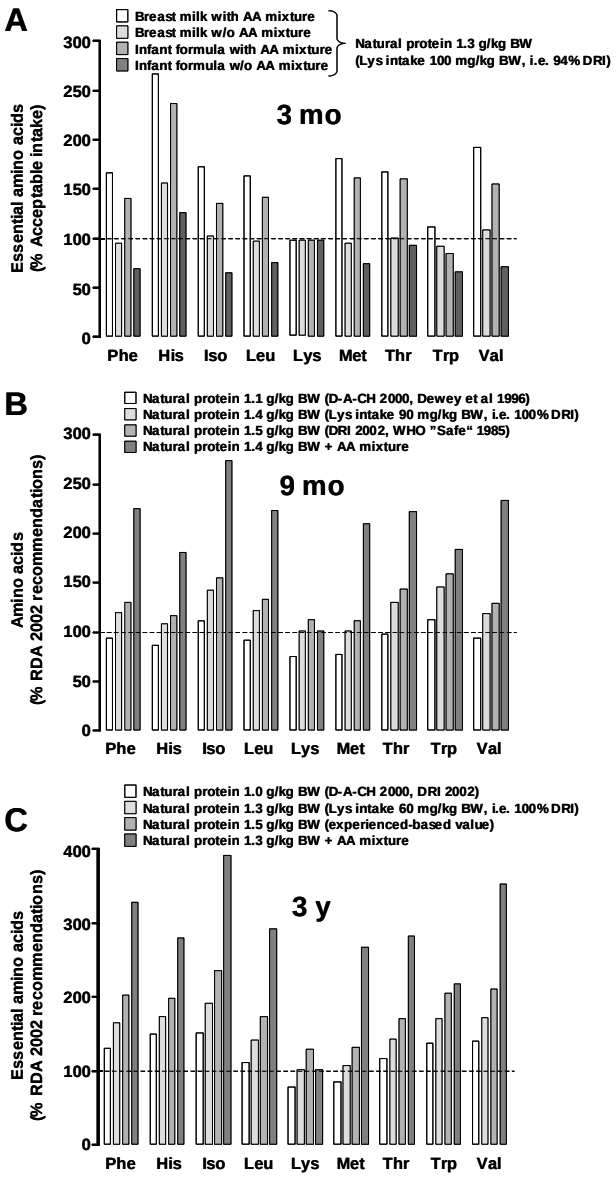

Figure 1. Impact of natural protein and Lys-free AA mixtures on intake of essential AA.

AA, Amno acids; *His*, histidine; *Iso,* isoleucine; *Lys,* lysine; *Met,* methionine and cystine; *Phe*, phenylalanine and tyrosine; *Thr,* threonine; *Trp,* tryptophan; *Val,* valine. Dotted lines indicate 100% of dietary recommendations (DRI recommendations[60]). All values are given as percentage of dietary requirements.

***A,* Age 3 months**. Natural protein intake was adjusted to 1.3 g/kg BW, Lys-free AA mixture accounted for 0.9 g protein/kg BW. Diet consisted of breast milk or infant formula.

***B,* Age 9 months**. Natural protein intake was varied from 1.1 to 1.5 g/kg BW according to D-A-CH[55], DRI[60], Dewey et al (1994)[57], and WHO "Safe" values[54]. AA mixture accounted for 0.8 g protein/kg BW. Values are given as percentage of DRI recommendations. Diet consisted of natural protein from milk (infant formula), cereals (semolina from wheat), potatoes, vegetables (carots), and fruit (banana).

***C,* Age 3 years**. Natural protein intake was varied from 0.9 to 1.5 g/kg BW according to DRI[60], D-A-CH[55], Dewey et al (1994)[57], and WHO "Safe" values[54]. Lys-free, Trp-redueced AA supplement accounted for 0.8 g protein/kg BW. Diet consisted of cereals (bread from wheat and rye), potatoes, vegetables (broccoli, tomatoes), fruits (banana, apple), and cow milk. Contents according to Müller and Kölker (2004).[62]

Annex 7
Influence of maintenance treatment on outcome

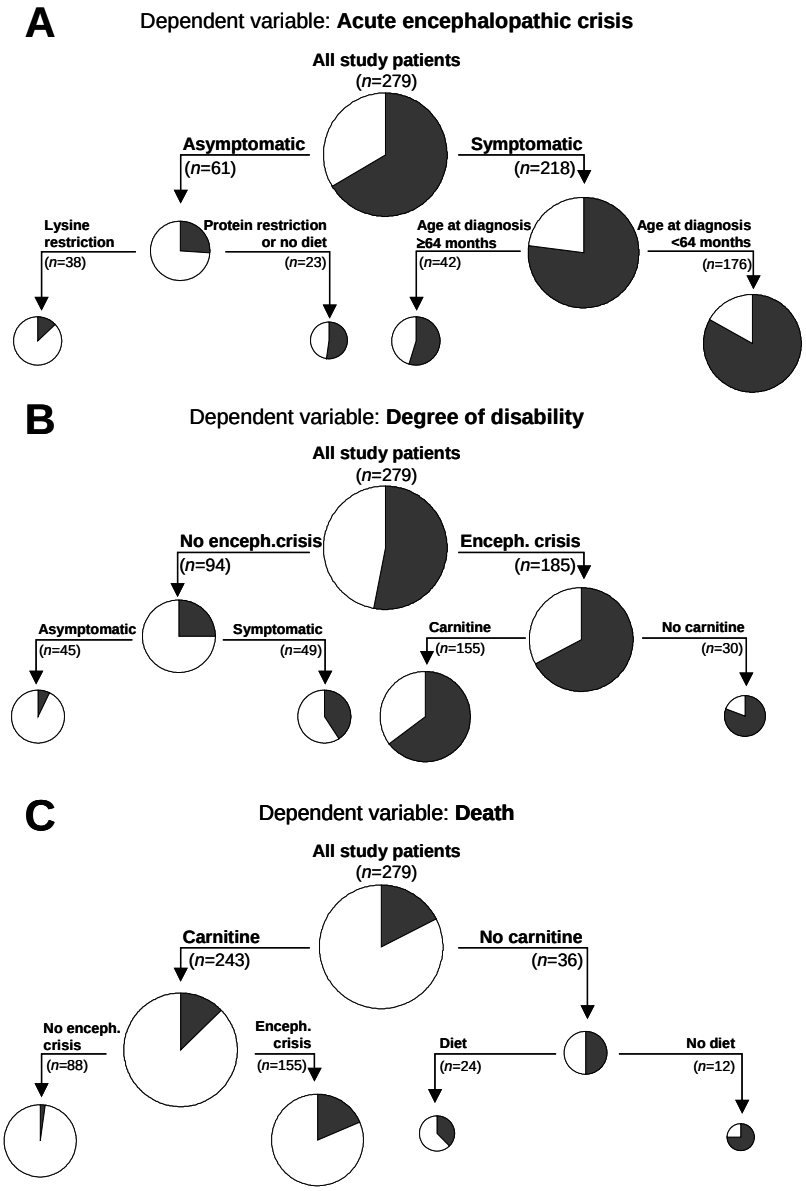

Figure 1. Cross-sectional study on 279 patients: Effect of diet and carnitine on outcome.

Classification-and-regression-tree (CART) analysis of treatment-dependent and -independent variables on different outcome variables demonstrated that dietary treatment (in particular Lys restriction) and carnitine supplementation improved the outcome, ie reduced the frequency of acute encephalopathic crises (***A***), and decreased the degree of disability (***B***) and death (***C***). Dietary treatment was less effective, if introduced after the manifestation of neurologic disease, whereas carnitine supplementation reduced the degree of disability and death rate also in these patients. The dark gray areas of each pie chart represent the percentage of patients in that subgroup who have suffered an encephalopathic crises (***A***) or deceased (***C***), or represent the degree of disability (**B**; white pie = no handicap [minimum]; dark gray pie = severe handicap [maximum]). The overall area of the pie chart indicates the size of each subgroup relative to the total population. To minimize the risk of overfitting information, the trees were cut after the second node. Results of an international cross-sectional study.[24]

Annex 8
International variability of outcome

Table 1. Acute encephalopathic crises in *pre-symptomatically* diagnosed GCDH patients.

Reference	Origin of patients	Patients	Encephalopathic crises
		(*n* =)	*(number of patients, [%])*
Hoffmann et al (1996)[1]	Europe	21	1 (**5%**)*
Strauss et al (2003)[3]	Amish (U.S.A.)	20	7 (**35%**)
Naughten et al (2004)[4]	Ireland	10	1 (**10%**)*
Kölker et al. (unpublished)[4]	Germany	10	1 (**10%**)[‡]
Cross-sectional study (unpublished)[5]	Europe, America, Asia, Africa	61	16 (**26%**)

Some patients have been included into two different studies.
Additional information of patients and cohorts:
Patient died from bronchopneumonia accompanied by vomiting with inappropriate management in a peripheral hospital. Furthermore, this patient was neurodevelopmentally delayed, had a complex perinatal history (neonatal sepsis, rickets of prematurity) and was preterm at 31 weeks gestation.
[‡] This patient suffered acute encephalopathic crises during a gastrointestinal infectious disease following delayed start of emergency treatment in another hospital.
Additional information on maintenance therapy:
[1] Maintenance treatment: *a)* lysine restriction *plus* lysine-free amino acid mixtures *plus* carnitine (13/21 patients) or *b)* only carnitine without dietary treatment (8/21). Only short-term follow-up has been investigated. The effect of dietary treatment was not systematically investigated.
[2] Maintenance treatment: protein restriction (*without* lysine-free amino acid mixtures) *plus* carnitine (in all patients) *plus* topiramate.
[3] Maintenance treatment: protein restriction (*without* lysine-free amino acid mixtures) *plus* carnitine *plus* supplemental powder (glutamine, creatine monohydrate, riboflavin, alpha-lipoic acid, coenzyme Q10, calcium panthothenate) *plus* pediatric vitamin mixture *plus* phenobarbital (in all patients).
[4] Maintenance treatment: lysine restriction *plus* lysine-free amino acid mixtures *plus* carnitine (in all patients)
[5] Maintenance treatment: *a)* lysine restriction *plus* lysine-free amino acid mixtures (38/61), *b)* protein restriction *without* lysine free amino acid mixtures (19/61), or *c) no* dietary treatment (4/61). All patients were treated with carnitine. Frequency of acute encephalopathic crisis was lower in group *a)* than in group *b)* and *c)*.

Table 2. Acute encephalopathic crises in *symptomatically* diagnosed GCDH patients.

Reference	Origin of patients	Patients	Encephalopathic crises
		(*n* =)	*(number of patients, [%])*
Hoffmann et al (1996)[23]	Europe	36	25 (**75 %**)*
Busquets et al (2000)[5]	Spain	42	24 (**57%**)[‡]
Strauss et al (2003)[29]	Amish (U.S.A.)	17	16 (**94 %**)
Naughten et al (2004)[28]	Ireland	11	11 (**100%**)
Kyllerman et al (2004)[26]	Scandinavia	27	24 (**89%**)[†]
Cross-sectional study[24]	Europe, America, Asia, Africa	218	169 (**78 %**)**

Some patients have been included into two different studies.
Nine patients (25%) were classified as “insidious-onset” type with slowly developing neurologic disease without apparent history of an acute encephalopathic crisis.
[‡] Insidious onset: 18 patients (43%).
[†] Insidious onset: 3 patients (11%).
** Insidious onset: 34 patients (16%).

Annex 9
Acute encephalopathic crises

A rational and practical approach to emergency treatment in GCDH deficiency necessitates a robust model. This should be based on all the evidence including a detailed description of the sequence of progressive clinical, neuroradiological and biochemical abnormalities observed during such crises as well as evidence from animal studies,[13,20,23,29-31,95-98] and a pathomechanistic understanding of this disease.[68] Clinically, first neurological symptoms usually develop after a 24 to 72-h history of a febrile illness with reduced oral intake of calories and fluids which induces catabolic state. **Vomiting** and **diarrhoea** considerably accelerate this process and are to be considered as dangerous. Characteristically, there is a continuum between the onset of an intercurrent illness and the first signs of a crisis and, thus, the onset of a crisis is difficult to predict precisely. Children quite often show **progressive reduction of consciousness** from alertness to somnolence, stupor, and, finally, (pre-) comatose state. Following a period of progressive clinical deterioration parents of affected children often precisely recollect the onset of motor dysfunction as abrupt or stroke-like (*"sudden head lag", "suddenly collapsed", "sudden loss of muscle tone"*). Usually, **profound muscular hypotonia** (or less frequently severe rigidity) is the first severe neurological sign which may be reversed if aggressive emergency treatment is implemented immediately. If treated insufficiently or if treatment is delayed, muscular hypotonia may improve over days and weeks at which time **dystonia, dyskinesia, and choreoathetosis** may appear and is usually irreversible. Acute onset of motor dysfunction may be accompanied by **seizures**.

Biochemically, the intracellular metabolism of affected children switches from an **anabolic to catabolic state**, resulting in further increased concentrations of glutaric and 3-hydroxyglutaric acids in body fluids due to increased lysine degradation. Signs of severe metabolic decompensation, such as hypoglycemia, lactic acidosis, hyperketosis, and hyperammonemia like in classical organic acidurias (eg methylmalonic, propionic acidurias) are typically absent or relatively mild during acute encephalopathic crises. Neuroradiologically, first abnormalities in the basal ganglia can be found using diffusion-weighted MRI[29,96,97,98] and later appear as increased signal intensity in T_2-weighted images.[20,29,30,95,97] Serial MRI studies also demonstrated the **temporospatial extension of basal ganglia injury**. Hyperintense lesions characteristically begin to spread from the dorsolateral aspects of the **putamen**, evolving in a ventromedial direction, sometimes also involving the **caudate heads** and the **globi pallidi**.[19,24,29] Shrinkage and volume loss of the basal ganglia subsequently develop during weeks and months. Pathomechanistically, the above mentioned changes can be explained at least in part by increased activation of the putamen via glutamatergic corticostriatal projections or direct stimulation of glutamatergic receptors, resulting in overactivation (muscular hypotonia) and subsequent neuronal damage (dystonia) in the putamen. Although the underlying mechanisms are not yet unravelled, the working hypothesis is that accumulating organic acids are responsible for the damage.[68,69]

Annex 10
Emergency treatment card

+ EMERGENCY CARD +

If this child presents to a medical office or emergency room, please make sure that he/she is assessed immediately by a pediatrician/physician.

Patient: ,	**Protocol updated:** / /
DOB: / /	**Approximate weight:** **kg**
Address: City Zip Code Street	
Phone:	**Handy:**

_____ has **glutaric aciduria type I** (synonyms, glutaric acidemia type I, glutaryl-CoA dehydrogenase deficiency), an inborn error of **lysine** and **tryptophan** metabolism due to deficiency of the enzyme mitochondrial glutaryl-CoA dehydrogenase. This disease puts him at risk for the following complications:

1. **Acute striatal injury (acute encephalitis-like encephalopathic crises)** precipitated by **catabolic state** (eg intercurrent febrile illness, immunisation, surgery**) from birth to age 6 years**
2. **Acute subdural hemorrhage** usually caused by minor head traumas
3. **Seizures**

NOTE: Striatal injury (acute encephalophatic crises) starts with **unspecific neurological signs** usually after a 24-72 h history of catabolic state (eg common childhood infection) and – if untreated – develops to irreversible striatal damage. Muscular hypotonia, rigidity, dystonia, depressed consciousness, and seizures should be regarded as **ALARMING SIGNS** and should prompt immediate hospitalisation and start of emergency treatment as outlined below.

At the earliest opportunity, the attending physician should contact _____'s metabolic specialist, Dr. _____, _____Hospital, at_____(office) or _____(reception).

In general, emergency treatment should start immediately and aggressively!

Emergency treatment aims at…

…reversing catabolic state by administration of high-energy fluids (plus insulin)r
…reducing organic acid production by transient reduction or omission of natural protein
…amplifying physiologic detoxifying mechanisms by carnitine supplementation and alkalination of urine
…preventing secondary carnitine depletion by carnitine supplementation
…balancing body fluids and pH state by rehydration and buffering

Inpatient emergency treatment should be performed as followed (most important strategies are highlighted using red or bold letters):

A. Energy requirement				
Calories	**Increase to at least 120% of age-dependent daily requirements**			
(kcal/kg BW/day)	0-6 mo	7-12 mo	1-3 y	4-6 y
	110-130	**100-110**	**100-110**	**100**
B. Intravenous infusions				
Glucose	**15(-20) g/kg BW/day i.v.**			
Lipids	**Start with 1-2 g/kg BW/day i.v.**, if possible increase stepwise to 2-3 g/kg BW/day			
Electrolytes	Electrolytes should be kept in the **upper normal range** (intermittent tubulopathy can occur during crises)			
Insulin	If **persistent hyperglycemia >150 mg/dl and/or glucosuria**, start with 0.05 IE insulin/kg/h i.v. and adjust the infusion rate according to serum glucose (cave! Increased intracellular uptake of potassium)			
L-Carnitine	**100 (-200) mg/kg BW/day i.v.**			
C. Protein intake				
Natural protein	**Stop for max 24 (-48) hours**, then reintroduce and increase stepwise until the amount of maintenance treatment within 3-4 days. If the child is on a low protein diet without AA mixture, increase protein within 1-2 days.			
AA mixtures (lysine-free)	If tolerated, **AA mixtures should be continued** according to maintenance therapy: 0.8-1.3 g/kg BW/day			
D. Additional drug therapy				
Antipyretics[§]	If temperature > 38.5 °C, e.g. ibuprofen 10-15 mg/kg BW per dose p.o.			
Antibiotics	Purposeful and timely administration			
Antiemetics	If vomiting; ondansetron 0.1 mg/kg BW per dose i.v. (max. 3 doses daily)			
Diuretics	If diuresis is less than 3-4 ml/kg/day; furosemide 0.5-1.0 mg/kg per dose i.v. (3-4 doses per day; cave! Rebound and electrolyte loss)			
Bicarbonate	If acidosis; alkalination of urine also facilitates urinary excretion of organic acids			
Antiepileptics	If seizures; start with phenobarbital and/or phenytoin			
E. Monitoring				
Blood	Glucose, blood gases, electrolytes, calcium, phosphate, complete blood cell count, creatinine, urea nitrogen, C-reactive protein, amino acids[‡], carnitine state, blood culture, amylase/lipase, creatine kinase.			
Urine	Ketone bodies, pH			
Vital signs	Heart rate, blood pressure, temperature, diuresis; Glasgow Coma Scale if reduced consciousness			
All calculations for A and B should be based on the expected and *not* on the actual weight!				

Annex 11
Clinical monitoring

GCDH deficiency								
Patient	*Name*		*Pre-Name*					
Address	*City*		*ZIP Code*		*Street*		*Number*	
GCDH gene mutations	[Father]		[Mother]					
GCDH enzyme analysis	*%resid. GCDH activity*							
Date	*DD/MM/YY*							
Investigator	*Name*							
Therapy								
Lysine	*mg/kg BW/day*							
Tryptophan	*mg/kg BW/day*							
Protein (total)	*g/kg BW/day*							
Protein (natural)	*g/kg BW/day*							
Energy	*kcal/kg BW/day*							
L-Carnitine	*mg/kg BW/day*							
Riboflavin	*mg/day*							
Others	*Please specify*							
Anthropometry								
Weight	*kg / P.*							
Height	*cm / P.*							
Head circumference	*cm / P.*							
Immune system								
Body temperature	*°C*							
Febrile illness (since last presentation)	*If yes, please specify*							
Vaccination (since last presentation)	*If yes, please specify*							
Skin and hair								
Acrodermatitis acidemica	*Tick if appropriate*							
Hair loss	*Tick if appropriate*							
Sweating	*Tick if appropriate*							
Others	*Short description*							

Neck								
Struma	*If yes, please specify*							
Chest								
Recurrent aspirations	*Tick if appropriate*							
Dyspnoea	*Tick if appropriate*							
GI tract								
Vomiting	*Tick if appropriate*							
Diarrhoea	*Tick if appropriate*							
Feeding problems	*Tick if appropriate*							
Tube feeding	*Tick if appropriate*							
Orofacial dyskinesia	*Tick if appropriate*							
Hepatomegaly	*Tick if appropriate*							
Nervous system								
Consciousness	*1(awake) – 4(coma)*							
Muscle tone	*Please specify*							
Head control	*Please specify*							
Monosynaptic reflexes	*0 (none) – 4+ (brisk)*							
Dystonia	*Tick if appropriate*							
Orofacial dyskinesia	*Tick if appropriate*							
Choreoathetosis	*Tick if appropriate*							
Other movement disorders	*If yes, please specify*							
Joint (sub-)luxations	*If yes, please specify*							
Joint contractures	*If yes, please specify*							
Can sit alone	*Yes or No*							
Can stand alone	*Yes or No*							
Can walk alone	*Yes or No*							
Weel-chair	*Yes or No*							
Fine motor skills	*Please specify*							
Use of language	*Please specify*							
Seizures	*Yes or No*							

Annex 12
Useful contact details and databases

This annex contains contact details for organisations which provide different levels of support and further information for patients and carers.

Arbeitsgemeinschaft für Pädiatrische Diätetik
Chairperson: Agnes van Teffelen-Heithoff

Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen (APS)
URL: http://www.aps-med.de/
Chairman: Prof. Dr. H.-G. Koch
E-mail: aps-vorstand@klinikum-braunschweig.de

Australasian Society for Inborn Error of Metabolism (ASIEM)

British Inherited Metabolic Disease Group (BIMDG)
URL: http://www.bimdg.org.uk/

Children Living with Inherited Metabolic Diseases (Climb)
URL: http://www.climb.org.uk/
Executive Director: S. Hannigan
E-mail: steve@climb.org.uk

Deutsche Dystoniegesellschaft e.V. (DGG)
URL: http://www.dystonie.com/

Dutch Society for Inborn Errors of Metabolism (ESN)

Garrod Association
URL: http://www.garrod.ca/
President: Prof. Dr. Dr. C. A. Rupar
E-mail: trupar@julian.uwo

International Organization of Glutaric Acidemia (IOGA)
URL: http://www.glutaricacidemia.org/
Director: M. Metil
E-mail: mmetil@helicon.net

International Society for Neonatal Screening (ISNS)
URL: http://www.isns-neoscreening.org/
President: Prof. Dr. J.-L. Dhondt
E-mail: dhondt.jeanlouis@ghicl.fupl.asso.fr

Italian Society for the Study of Inherited Metabolic Diseases (SISMME)
URL: http://www.sismme.it/
President: Prof. Dr. Alberto B. Burlina
E-mail: burlina@pediatria.unipd.it

Metab-L
URL: http://www.daneel.franken.de/metab-l/
Contact and list maintainer: Dr. C. Renner
E-mail: cjrenner@well.com

METABNET – Network for Genetic Metabolic Diseases Detectable by Newborn Screening
URL: http://www.metabnet.de
Coordinator: Dr. P. Burgard
E-mail: p.burgard@metabnet.de

Online Mendelian Inheritance of Man (OMIM)

URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

Organic Acidemia Association
URL: http://www.oaanews.org/
E-mail: OAANews@aol.com

Orphanet
URL: http://www.orpha.net/

PubMed
URL: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Limits&DB=pubmed

Japanese Society for Inherited Metabolic Diseases (JSIMD)
URL: http://www.jsimd.org/

Red Latinoamericana Enfermedades Metabolicas Hereditarias (REDLAEM)
URL: http://www.unam.mx/redlaem/

Selbsthilfegruppe Glutarazidurie e.V.
URL: http://www.glutarazidurie.de/
Chairman: A. Schaal
E-mail: glutara@aol.com

Society for Inherited Metabolic Diseases (SIMD)
URL: http://www.simd.org
E-mail (SIMD administrator): lublinkl@ohsu.edu

Society for the Study of Inborn Errors of Metabolism (SSIEM)
URL: http://www.ssiem.org.uk/

Societé Francaise pour l'étude des erreurs innées du métabolisme (SFEIM)
URL : http://www.sfpediatrie.com/
President : Prof. Dr. G. Touati

Annex 13
Evidence table of systematic literature review

Level 1++, 1+, 1-, 2++. None

Level 2+. Evidence from well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.

Authors	Title	Study design	Results / Conclusions
Kölker et al, *submitted.*	Natural history, outcome, and treatment efficacy in glutaryl-CoA dehydrogenase deficiency.	Study design: - Questionaire-based evaluation of *n*=279 patients from Europe, America, Africa and Asia. Data collection on treatment-dependent and –independent variables. - Non-parametric statistical analysis; CART analysis to assess the impact of single variables on outcome parameters.	**Mode of diagnosis** - *n*=61 asymptomatic patients (neonatal screening, high-risk screening, siblings, macrocephaly); *n*=218 symptomatic patients (acute encephalopathic crisis, insidious-onset) **Acute encephalopathic crisis** - The majority of crises occurred until age 3 years; no crisis was reported after age 6 years; - Most patients (70%) had only one crisis and revealed a moderate to severe movement disorder. **Mortality** - Approximately 20% of all patients died. - The cause of death remained often unknown, pneumonia was the most frequently considered cause of death; - Deceased patients showed the highest morbidity score and the highest number of acute crises. **Variables that influence the outcome** **Positive effect:** - Early diagnosis (< 3 months of age), i.e. before the window for acute striatal damage opens - Oral carnitine supplementation - Lysine-restricted diet **No effect:** - Riboflavin - Protein-restricted diet **Not evaluated:** - Emergency treatment could not be evaluated by this approach, since important parameters (hours of delay, exact protocols used) remained unknown in included patients. **Genotype phenotype correlation** - No correlation between residual GCDH deficiency and neurological outcome. **Open questions** - Nature of insidious-onset type (distinct disease course or abortive crisis); - Individual risk and protection factors to suffer an acute crisis.

Level 2-. Evidence from case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.

Authors	Title	Study design	Results / Conclusions
Bjugstad et al (2000) J Pediatr 137 : 681-686.	Age at symptom onset predicts severity of motor impairment and clinical onset of glutaric aciduria type I.	Study design: - Meta-analysis of previously published case reports and cohort studies (*n*=42 articles). - Multiple regression analysis ; *n*=115 patients	**Encephalopathic crises** - 87 % of encephalopathic crises occur until age 24 months; age at onset predicts severity of neurologic disease. **Treatment and Monitoring** - Treatment has no benefit in symptomatic patients; - No statement on benefit in asymptomatic patients (not enough available data); - No statement on emergency treatment; - No statement on monitoring.
Busquets et al (2000) Pediatr	Glutaryl-CoA dehydrogenase	Study design: - Cohort study of 43 Spanish patients	**Biochemical and clinical presentation** - *n*=26 high excretors (A293T, R402W),

Res 48 : 315-322.	deficiency in Spain: evidence of two groups of patients, genetically and biochemically distinct.	(from 35 unrelated families) - Evaluation of disease course (acute encephalopathy versus insidious onset) and severity of disability - Correlation of genotypes and biochemical and clinical phenotypes - No assessment of follow-up - No evaluation of therapy	*n*=17 low excretors (V400M, R227P), *n*=24 with acute encephalopathic crises, *n*=18 patients with insidious-onset type, 71% of low excretors and 50% of high excretors showed a 'severe' clinical phenotype, - 91% of patients with an encephalopathic crisis presented with a 'severe' clinical phenotype. **Conclusion** - Two genetically and biochemically distinct subgroups in Spain, - Severity of clinical phenotype is closely linked to development of encephalopathic crises rather than to residual enzyme activity or genotype.
Hoffmann et al (1996) Neuropediatrics 27: 115-123. → see also: Hoffmann et al (1991)	Clinical course, early diagnosis, treatment, and prevention of disease in glutaryl-CoA dehydrogenase deficiency.	Study design: - Retrospective analysis in Europe; - *n*=21 pre-symptomatic children (mean age at diagnosis: 12 mo, range 0-120 mo); - *n*=36 symptomatic children (mean age at diagnosis: 27 months, range 3-173 mo); **- Treatment:** **a) Well-day treatment:** - No definite treatment protocol (*n*=13 of asymptomatic patients received lysine/tryptophan-restricted diet, whereas *n*=8 received moderate protein restriction or even no diet); - Carnitine supplementation (dosage ?) - No riboflavin (no sensitivity) **b) Emergency treatment:** - Glucose and electrolyte infusion (no exact protocol published), - Fever control/antipyretics - Carnitine dosagenot specified.	**Clinical presentation** **a) Pre-symptomatic children**: - 20/21 remained asymptomatic; 1/21 died (see also Monvari and Naughten 2000) using emergency treatment and carnitine supplementation - "The importance for dietary therapy remains unclear and needs further evaluation". **b) Symptomatic children**: - No clear benefit (but further neurologic deteroriation may have been prevented) 1/78 asymptomatic, 13/78 moderate handicap, 64/78 severe handicap, 16/78 died; - Neurological deterioriation: Insidious-onset type 19%, encephalopathic crisis 81%. **Monitoring**: - Risk of tryptophan depletion using lysine- and tryptophan-reduced diet if not monitored.
Monavari and Naughten (2000) Arch Dis Child 82: 67-70. → see also: Naughten et al (2004); Twomey et al (2003)	Prevention of cerebral palsy in glutaric aciduria type I by dietary management	Study design: - Prospective follow-up study in Ireland, - *n*=6 asymptomatic patients, - *n*=6 symptomatic patients; Treatment: → See Naughten et al (2004)	**Outcome** **a) Asymptomatic patients**: 1/6 crises, 4/6 no neurologic abnormality, 1/6 fluctuating neurologic problems, 1/10 died (pneumonia, no adequate emergency treatment, prematurity, placenta previa); **b) Symptomatic patients**: 6/6 movement disorders, 5/6 died
Naughten et al (2004) J Inherit Metab Dis 27: 917-920. → see also: Monavari and Naughten (2000); Twomey et al (2003)	Glutaric Aciduria Type I, Outcome in the Republic of Ireland	Study design: - Prospective follow-up study in Ireland (1988-2004; 16 years), - *n*=10 asymptomatic patients, - *n*=11 symptomatic patients; Treatment: **Well-day treatment:** - Protein restriction (0.5-2.0 g/kg/d), AA mixture (total protein: 1.5-3.0 g/kg/d); - Carnitine 100 mg/kg/d - No riboflavin (no patient was riboflavin-sensitive) **Emergency treatment:** - Stop natural protein (24-48 h), continue AA (p.o. or i.v.), - Increase energy intake (120%), - Double carnitine (200 mg/kg/d) **Monitoring:** - Regular (no definite time schedule given); - Anthropometrics; - OA (urine), FC (serum), AA (plasma); - MRI/CCT: 1 scan / year.	**Outcome** **a) Asymptomatic patients**: 1/10 crises, 6/10 no neurologic abnormality, 4/10 fluctuating neurologic problems (e.g. ataxia, delayed speech development), 1/10 died (pneumonia, no adequate emergency treatment, prematurity, placenta previa); **b) Symptomatic patients**: 10/11 movement disorders, 7/11 died **Conclusions** - Symptomatic patients had a poor outcome despite aggressive treatment (treatment may prevent a more rapid deterioration); - Asymptomatic patients had a good outcome with aggressive treatment (see also comment of Leonard and Collins: aggressive emergency treatment might be helpful whereas the benefit of diet is not proven); - No helpful biochemical marker for monitoring is known.
Strauss et al (2003) Am J Med Genet 121C:38-52. → see also: Morton et al (1991)	Type I glutaric aciduria, part 1: Natural history of 77 patients	Study design: - Progressive follow-up study in the U.S.A. (1988-2002; 14 years), a) *n*=40 Non-Amish (all symptomatic), b) *n*=37 Amish (*n*=17 symptomatic, *n*=20 pre-symptomatic); - *n*=57 symptomatic, *n*=20 pre-symptomatic	**Basal ganglia injury:** a) Symptomatic: 85 % (non-Amish) – 94 % (Amish) b) Pre-symptomatic: 35 % (Amish) **Degree of motor disability:** a) Symptomatic (Amish and non-Amish): 12 % asymptomatic, 14% subtle and mild, 74 % moderate and severe,

		Well-day treatment: - Natural protein (1-1.25 g/kg/d), - Calories 100-115 kcal/kg/d; - Carnitine 100 mg/kg/d - Riboflavin 10 mg/kg/d - Additional treatment: Creatine (100mg/kg/d), glutamine (100mg/kg/d), alpha-lipoic acid (10 mg/kg/d), coenzyme Q (8.4 mg/kg/d), panthothenic acid (5.6 mg/kg/d), alpha-linolenic acid (150 mg/kg/d), phenobarbital (4-6 mg/kg/d), ibuprofen (10-15 mg/kg q6 h) if fever and inflammation, montekulast (5-10 mg/kg/d) if inflammatory disease, ondansetron (0.15 mg/kg q8 h) if vomiting - No riboflavin (no patient was riboflavin-sensitive) **Emergency treatment:** - Stop all protein intake, - Carnitine IV 400 mg/kg/d - Identify and treat infections, - Dextrose therapy: 8-10 mg/kg/min IV (plus insulin if necessary), - Alkalize urine, output > 4 ml/kg/h (lasix 0.5-1 mg/kg/dose if necessary), - Sedation and neuroprotection: phenobarbital, fosfenytoin, consider N-acetylcysteine, - Measures to reduced CSF production and ICP: lasix, acetazolamide.	b) Pre-symptomatic (Amish): 65 % asymptomatic, 9% subtle and mild, 26 % moderate and severe. **Acute encephalopathic crises :** Occurred until age 18 months

Level 3. Non-analytical studies, e.g. case reports, case series

Authors	Title	Study design	Results / Conclusions
Bennett et al (1986) → see also : Bjugstad et al (2000)	Glutaric aciduria type 1: Biochemical investigations and post mortem findings.	Study design: - Case report (*n*=1) and post mortem examination of a fatal course of the disease.	**Clinical presentation and therapy** - Confirmation of diagnosis after acute encephalopathy crisis at age 6 months - Successful biochemical control was achieved using a lysine- and tryptophan-restricted diet. - Death occurred at 10.5 months with a bronchopneumonia. **Post mortem examination** - CNS: mild gyral atrophy with atrophy of caudate nucleus; fatty infiltration of liver, kidneys, and heart. - Glutaric acid (frontal cortex): 40 µmol/L (i.e. more than 10-fold lower than in untreated *post mortem* cases)
Bodamer et al (2004) J Inherit Metab Dis 27 : 877-883.	Nuclear magnetic resonance spectroscopy in glutaryl-CoA dehydrogenase deficiency.	Study design: - Magnetic resonance imaging and spectroscopy in *n*=1 patient (adult-onset type GA-I) presenting with a leukoencephalopathy	**Neuroradiological findings** - Elevated levels of intracerebral lactate and elevated choline/N –acetylaspartate ratios in areas with severe white matter abnormalities; - normal spectra in basal ganglia **Conclusion** - Increased myelin turnover and reduced neuronal integrity in periventricular white matter
Brandt et al (1979) J Pediatr 94: 669-673. → see also: Bjugstad et al (2000)	Treatment of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria).	Study design: - Intervention study (each 1 week: Lys/Trp-reduced diet, low-protein diet, riboflavin - *n*=3 symptomatic patients - Determination of biochemical response (GA, 3-OH-GA, glycine, 2-amino-adipic acid) - Clinical response: no standardized measurements, subjective scale	**Response to treatment** - Biochemical response to Lys/Trp-reduced, low-protein diet, and riboflavine; - "difficulties to accept Lys/Trp-reduced diet" - Clinical improvement during low-protein and Lys/Trp-reduced diet (1 week!), no long-term follow-up data; - No carnitine, no emergency treatment; **Conclusion** - Low-protein diet and riboflavin is recommended for diet
Brismar and Ozand (1995) Am J Neuroradiol; 16:	CT and MR of the brain in glutaric aciemia type I: a review of 59	Study design: - Clinical and neuroradiological investigations in GCDH deficiency - Report on *n*=5 prospectively followed	**Clinical findings** - In half the patients macrocephaly was present, and in half the onset was acute, often following infection and mimicking

675-683.	published cases and a report of 5 new patients.	patients - Review on *n*=59 patients	encephalitis. **Neuroradiological findings** - Brain atrophy or hypoplasia: 61% - White matter changes: 51% - Open opercula (usually very widely open) and often also wide cerebrospinal fluid spaces anterior to the temporal lobes: 93%. - Basal ganglia lesions (presenting as volume loss and high T2 signal in the caudate head and often also the lentiform nucleus bilaterally): 44% - Extracerebral fluid collections: 10% **Conclusion** - The finding of very widely open opercula suggests GCDH deficiency, and if combined with basal ganglia lesions is almost pathognomonic, especially in a child with macrocephaly.
Burlina et al (2004) J Inherit Metab Dis 27 : 911-915.	Management of movement disorders in glutaryl-CoA dehydrogenase deficiency : Anticholinergic drugs and botulinum toxin as additional therapeutic options.	Study design: Follow-up study on 4 Italian patients - Evaluation of movement disorders after symptomatic treatment with different drugs	**Response to treatment** - Anticholinergic drugs and botulinum toxin A were well tolerated and had a positive influence on the treatment on generalized and focal dystonia of affected children.
Chow et al (1988) Acta Neuropathol 76 : 590-594. → see also: Bjugstad et al (2000)	Neuropathology in glutaric acidaemia type I.	Study design: - Case reports and *post mortem* examinations in three children (2.5- 9 years of age) with fatal disease course.	**Clinical presentation and therapy** - Acute encephalopathic crises occurred at 5-17 months of age, resulting in dystonia. - Treatment was inconsistent: lysine-restricted diet (case 1), no treatment (case 2), baclofen and riboflavin (case 3). No neurological improvement was found in any of these children. - Cause of death: epileptic state (case 1), bronchopneumonia (case 3), unknown (case 3) **Post mortem examination** - Brain weights were normal - Putamina and globi pallidi were shrunken. Histology showed marked loss of neurons in the striatum associated with gliosis; scattered neurons were usually of the large type. - Marked spongiform changes in the white matter at many sites.
Desai et al (2003) Invest Radiol 38 : 489-496.	Magnetic resonance imaging of the brain in glutaric aciduria type I.	Study design: - MRI study in *n*=4 childen - Review of the literature	**Neuroradiological findings** - Abnormal increased signal intensity putamen and globus pallidus in all cases. - Involvement of caudate nucleus was minimal or absent - 15 months and older, FLAIR improved recognition of basal ganglia and white matter abnormalities. **Conclusion** - Abnormalities of the caudate nucleus may be not as prominent as previously suggested; FLAIR scans should be used at age > 15 months.
Elster (2004) J Comput Assist Tomogr 28: 98-100.	Value of diffusion-weighted resonance imaging for diagnosing acute striatal necrosis.	Study design: - Comparative study on CCT and MRI (T1, T2, DWI, MRS) - *n*=1 child	**Neuroradiological findings** - **CCT**: only subtle basal ganglia abnormalities; - **T2**: lesions in putamina; DWI: lesions in putamina, caudate nuclei and pallida; - **MRS**: no abnormality **Conclusion** - DWI is most sensitive to detect acute striatal injury in GCDH deficiency.
Fernandez-Alvarez et (2003) Mov Disord 18: 1076-1079.	Hand tremor and orofacial dyskinesia : clinical manifestation of glutaric aciduria type I in a young girl.	Study design: - Case report (*n*=1)	- Late-onset neurologic disease (tremor, orofacial dyskinesia) in a 16-year old female adolescent - MRI: Small lesion of dorsolateral aspects of putamen, leukoencephalopathy (preferentially of frontal areas)
Forstner et al	Glutaric aciduria	Study design:	**Neuroradiological findings**

(1999) Pediatr Radiol 29 : 138-143.	type I: ultrasonographic demonstration of early signs.	- Comparative study on US, CCT and MRI - *n*=6 children	- Macrocephaly was found in all patients, being present in three children at birth or developing rapidly within the first weeks of life. **- US** showed, in all patients, bilateral symmetrical cyst-like dilatation of the sylvian fissures. Progressive fronto-temporal atrophy developed within the first months. **- CT and MRI** demonstrated fronto-temporal atrophy with lack of opercularisation in all cases and basal ganglia or periventricular hypodensities in three patients. **Conclusions** - US should be performed as the primary imaging modality. - Cyst-like bilateral widening of the sylvian fissures is the first sign of GA-I, followed by progressive fronto-temporal and ventricular enlargement.
Funk et al (2005) Brain 128 : 711-722.	Neuropathological, biochemical, and molecular findings in a glutaric aciduria type 1 cohort.	Study design: - Case reports (*n*=6) and *post mortem* examinations in a cohort of Oji-Cree patients (8 months to 40 years of age) with fatal disease course. All patients were homozygous for the Oji-Cree mutation (IVS-1 $^{+5g>t}$).	**Clinical presentation and therapy** - Acute encephalopathic crises occurred from 4 to 10.5 months of age, resulting in movement disorders. - Treatment was performed inconsistently. - Dietary treatment was not used. **Post mortem examination** - CNS: Increased brain weight at different degree. - All patients had striatal atrophy with severe loss of medium-spiny neurons and mild loss of large striatal neurons. - Spongiform white matter changes were restricted to the brainstem. - Glutaric acid (all regions): approx. 600-3,200 µmol/L; 3-hydroxyglutaric acid (all regions): approx. 40-110 µmol/L.
Goodman et al (1975) Biochem Med 12 : 12-21. → see also: Bjugstad et al (2000)	Glutaric aciduria: a 'new' inborn error of amino acid metabolism.	Study design: - Presentation of the two index cases (brother and sister) with this disease.	**Clinical presentation** - Description of a novel neurodegenerative disease starting at about 6 months of age and characterized by opisthotonus, dystonia, and athetoid posturing. **Biochemical presentation** - Urinary excretion of glutaric acid, which was increased by oral administration of L-lysine. Inherited deficiency of glutaryl-CoA dehydrogenase deficiency was suggested as underlying reason.
Goodman et al (1977) J Pediatr 90 : 746-750. → see also: Bjugstad et al (2000)	Glutaric aciduria: Biochemical and morphologic considerations.	Study design: - Case report and first published *post mortem* examination in one child (age 10 years) with fatal disease course.	**Clinical presentation and therapy** - Acute encephalopathic crisis at age 7.5 months, resulting in dystonia and mental retardation. - Diagnosis was not made before age 7.5 years. No specific therapy (e.g. diet, carnitine, riboflavine) was performed. - Numerous hospitalizatons due to episodes of high fever, vomiting, and diarrhea. - The patient died during an episode of recurrent vomiting, increasing lethargy, hepatomegaly, resembling Reye-like syndrome. **Post mortem examination** - CNS: Increased brain weight, cerebral edema. 75% of the putamen (and lateral margins of caudate) showed severe neuronal loss and fibrous gliosis. Glutarate concentration (frontal cortex): approx. 1,000 µmol/L. **-** Fatty changes in liver, kidney, and myocardium.
Greenberg et al (2002) Mol Gen Metab 75:70-78. → see also: Haworth	Outcome of the three years of a DNA-based neonatal screening program for glutaric	Study design: Prospective follow-up study in Canada, *n*=4 asymptomatic patients Treatment: **Well-day treatment**:	- Description of DNA-based high-risk screening in a low excretor cohort (Oji-Cree) - 3 of 4 patients (one infant died) suffered acute encephalopathic crises despite

et al (1991); Funk et al (2005)	aciduria type I in Manitoba and Northwestern Ontaria, Canada.	Protein restriction (1.5 g/kg/d), Carnitine (50-100 mg/kg/d), Riboflavin 100 mg/d; **b) Emergency treatment**; **c) Additional treatment:** in one child: vitamin E, topiramate Monitoring: "1.5 times maintenance fluid, adequate calories…high dose intravenous carnitine, and pharmacological doses of riboflavin" (no exact protocol specified).	treatment (personal communication 5 / 5 patients suffered crises, C. R. Greenberg); - No statement on monitoring
Hald et al (1991) Am J Neuroradiol 12: 407-409.	Bilateral arachnoid cysts of the temporal fossa in four children with glutaric aciduria type I.	Study design: Comparative study on CCT and MRI - *n*=5 children	**Neuroradiological findings** - Four of the patients had findings consistent with bilateral arachnoid cysts of the temporal fossa. **Conclusion** - The observed association between temporal fluid collections and glutaric aciduria type I suggests that patients with bilateral arachnoid cysts should be investigated for this metabolic disorder.
Hartley et al (2001) Pediatrics 107: 174-175.	Glutaric aciduria type 1 and nonaccidental head injury.	Study design: - Case report (*n*=1)	- Subdural hemorrhages in a child with GA-I; discussion on the differential diagnosis of non-accidential head injury.
Haworth et al (1991) J Pediatr 118: 52-58. → see also: Bjugstad et al (2000); Funk et al (2005); Greenberg et al (2002)	Phenotypic variability in glutaric aciduria type I: report of fourteen cases in five Canadian Indian kindreds	Study design: - *n*=14 symptomatic patients dietary treatment (short-term, not continued, not specified, no specification of carnitine and riboflavin) - biochemical and clinical response (both not specified)	**Treatment** - No biochemical or clinical response to dietary treatment; diet was discontinued - High frequency of early deaths: 4/14 pts (9-17 mo), high variability of the other children, no long-term follow-up **Conclusion** Dietary treatment is not recommended; no statement on carnitine, riboflavin or emergency treatment
Hoffmann et al (1991) Pediatr 88: 1194-1203 → see also: Bjugstad et al (2000); Hoffmann et al (1996)	Glutaryl-coenzyme A dehydrogenase deficiency: a distinct encephalopathy.	Study design: - *n*=11 patients (9 symptomatic, 2 presymptomatic), - No standard treatment: low-protein diet and/or Lys/Trp-reduced diet, supplementation of carnitine (30-200 mg/kg/d) and riboflavin; no emergency treatment; - Biochemical response determined by GA concentrations (urine, plasma, CSF); - Clinical response: no standardized evaluation, appearance of encephalopathic crises.	**Biochemistry** - Biochemical response to lysine restriction (40-50 mg/kg/d)→ decrease of GA excretion, slighty reduction or no reduction in plasma and CSF - Carnitine supplementation: normalization of carnitine depletion - Side effects of tryptophan discussed **Outcome** - Symptomatic children: 1 slight improvement, no further crises, no further deterioration in the rest of this group; no encephalopathic crises and normal development in pre-symptomatic children **Conclusion** - Recommendations for treatment: Lys-restricted diet, carnitine supplementation, no Trp restriction due to side effects; no statement on emergency treatment
Iafolla et al (1989) J Pediatr 114: 1004-1006. → see also: Bjugstad et al (2000)	Megalencephaly in the neonatal period as the initial manifestation of glutaric aciduria type I.	Study design: - Case report (n=1 pre-symptomatic patient); Lys/Trp-restricted diet, supplementation of carnitine and riboflavin; no emergency treatment; 14 mo follow-up	- No encephalopathic crisis during the follow-up interval; - Conclusion: early diagnosis and treatment as chance for preventing neurologic deterioration
Jamjoom et al (1995) J Neurosurg 82 : 1078-1081.	Bilateral arachnoid cysts of the sylvian region in female siblings with glutaric aciduria type I. Report of two cases.	Study design: - Case report (*n*=2)	- Two sisters with macrocephaly, delayed motor development, bilateral arachnoid cysts of the sylvian region (CCT). - Surgery: Cystoperitoneal shunting of the larger cysts resulted in considerable neurological improvement in both children (no long-term follow-up). - Diagnosis was just made afterwards - Conclusions: Association of bilateral arachnoid cysts with GA-I.
Köhler and Hoffmann (1998) Pediatr Radiol 28: 582	Subdural haematoma in a child with glutaric aciduria type I.	Study design: - Case report (*n*=1)	- Subdural hemorrhage and retinal bleeding in a boy with previously diagnosis of GA-I most likely due to minor head trauma. - Discussion on shaken-baby syndrome as relevant differential diagnosis
Kölker et al	Acute	Study design:	- Acute encephalopathic crisis despite

(2001) J Pediatr 138: 277-279.	encephalopathy despite early therapy in a patient with homozygosity for E365K in the glutaryl-CoA dehydrogenase gene.	- Case report (*n*=1), - Turkish boy, diagnosed and treated early (diagnosed due to macrocephaly); - Lysine-restricted diet, carnitine and emergency treatment	early treatment with lysine-restricted diet and carnitine (it has been found out later that this family showed a poor compliance, unpublished observation).
Kölker et al (2003) Neuropediatrics ; 34 : 253-260.	Glutaryl-CoA dehydrogenase deficiency: Regional-specific analysis of organic acids and acylcarnitines in *post mortem* brain predicts vulnerability of the putamen.	Study design: - Case report and *post mortem* examination in one adolescent (age 14 years) with fatal disease course.	**Clinical presentation and therapy** - Acute encephalopathic crisis occurred at age 6 months, resulting in severe dystonia. **Treatment** - Lysine- and tryptophan restricted diet was performed and revealed a strong biochemical response (determined by urinary excretion of glutaric acid), whereas vigabatrin and riboflavin revealed no positive biochemical response. **Post mortem examination** - Increased brain weight, necrosis and severe neuronal loss with reactive astrogliosis in the striatum; spongiform changes in the white matter were moderate. **-** Glutaric acid and 3-hydroxyglutaric acids were up to 10 µmol/L in the CNS with highest 3-hydroxyglutaric acid concentration in putamen.
Külkens et al (2005) Neurology; 64: 2142-2144.	Late-onset neurologic disease in glutaryl-CoA dehydrogenase deficiency.	Study design: Report on *n*=2 cases (age 15 and 66 years) with late-onset neurologic disease, presenting with leukoencephalopathy and an atypical neurologic-psychiatric symptomatology. - Review on 5 cases with suggested adult-onset type GCDH deficiency.	**Clinical presentation** - Severe headaches, gait disturbances (ataxia), tremor, vertigo, halluzinations, focal epilepsy, dementia. - Partial improvement (older patient) or complete recovery (younger patient) after implementation of mild protein restriction and oral carnitine supplementation. **MRI / MRS** - Leukoencephalopathy (frontal > occipital), periventricular but not sparing U fibres; older patient also revealed general atrophy. - Basal ganglia appeared normal. MRS (younger patient) revealed elevated lactate in areas with severe white matter changes. **Diagnostic work-up** - Mutation analysis demonstrated homozygosity for two previously known disease-causing mutations (R88C, R383C) resulting in residual GCDH activity of < 1% and massive excretion of organic acids (high excretors) - *Ultima ratio* brain biopsy (older patient) demonstrated no leukodystrophy but edematic swelling of tissue. - Concentrations of glutaric acid (approx. 5,000 µmol/L) and 3-hydroxyglutaric acid (appr. 200 µmol/L) were massively elevated.
Kurul et al (2004) Pedatr Neurol 31: 228-231.	Glutaric aciduria type 1: proton resonance spectroscopy findings.	Study design: - Case report (n=1), magnetic resonance spectroscopy	- MRS of frontal white matter and lentiform nuclei revealed decreased N-acetylaspartate/creatine ratio, slightly increased choline/creatine ratio, and increased myoinositol/creatine ratio - Conclusion: indicates neuroaxonal damage, demyelination, and astrocytosis in these areas.
Kyllerman and Steen (1980) Arch Pediatr 37; 279.	A “common” metabolic disorder?	Study design: Estimation of prevalence in Sweden	- Prevalence of GCDH deficiency in Sweden was estimated to 1 in 30,000 newborns.
Kyllerman et al (1994) Mov Disord 9: 22-30 → see also: Bjugstad et al (2000); Kyllerman et al (2004)	Dystonia and dyskinesia in glutaric aciduria type I: Clinical heterogeneity and therapeutic considerations	Study design: - Retrospective analysis of 12 patients (age 9 months to 16 years) from Sweden and Norway. Evaluation of neurological outcome. Review on 57 pooled cases. → See also Kyllerman et (2004).	**Movement disorders** **a) Sweden/Norway:** - 10/12 dystonic-dyskinetic disorder, 1/12 mild motor dysfunction, 1/12 asymptomatic**.** **b) Review on 57 pooled cases:** - 77% severe dystonia, 10% mild

			extrapyramidal syndrome, 12% asymptomatic (the authors suggested that this disorder may go undetected in the cerebral palsy and mentally retarded child and adult populations) **Deaths** - Two children in state of hyperthermia **Feeding problems** - Carnitine and malnutrition developed in patients with severe dystonia and dysphagia which necessitated replacement therapy and gastrostomy. **Neuroradiology** - CCT/MRI: 7/10 deep bitemporal spaces **Neuropsychological testing** - 8/12 receptive language function superior to expressive language and motor function
Kyllerman et al (2004) Eur J Paediatr Neurol. 8 :121-129. → see also: Kyllerman et (1994)	Long-term follow-up, neurological outcome and survival rate in 28 Nordic patients with glutaric aciduria type 1.	Study design: - Retrospective analysis of 28 Scandinavian patients diagnosed between 1975 – 2001. - *n*=25 symptomatic patients, - *n*=3 siblings; - Median follow-up: 14 years - Treatment: Dietary treatment (protein restriction or lysine- and tryptophan-restricted diet), carnitine, and riboflavin: evaluation of the benefit from different therapies for movement disorders.	**Morbidity** - Six patients died (21%) - At 10 years of age the cumulative survival rate was 89% and at 35 years 44%. **Movement disorders** - Dystonia (n=20), dyskinesia (n=4), slight spastic signs (n=3) **Acute encephalopathic crises** - The onset was acute encephalopathic in 24 patients and insidious in 3. **Treatment** - Neurological deficits did not improve on the offered treatment (diet, carnitine, riboflavine). - Deterioration may have been averted by intense acute metabolic treatment in a few patients.
Lindner et al (2004) J Inherit Metab Dis 27: 851-859.	Neonatal screening for glutaryl-CoA dehydrogenase deficiency.	Study design: - MS/MS screening results in GA-I (n=6) and short-term follow-up of C5DC and C5DC/C8 and C5DC/C16 ratios - Review of the literature on prevalence of GA-I and diagnostic pitfalls	- C5DC, C5DC/C8 and C5DC/16 were clearly elevated initially and during short-term follow-up (up to 100 days) in all six children using MS/MS - Report on DNA-based neonatal screening in the Oji-Cree, a Canadian low excretor cohort with a single intron mutation
Lipkin et al (1988) J Pediatr 112 : 62-65. → see also: Bjugstad et al (2000)	A case of glutaric aciduria type I: effect of riboflavin and carnitine.	Study design: - Case report (n=1), - 5-year-old boy (USA), diagnosed at age 45 months after progressive neurological deterioration following two acute encephalopathic crises; treatment with moderate protein restriction (1.5 g/kg/day), riboflavin (100 mg/day), and L-carnitine (100 mg/kg/day); determination of biochemical and clinical response.	**Biochemical response** - Riboflavin: increase in GABA but no decrease of glutaric acid levels in CSF - Carnitine: Increase in total carnitine (plasma), increase in short-chain acylcarnitines (urine, <1% of oral carnitine) **Clinical response** - Modest clinical improvement with long-term treatment with carnitine and riboflavin (no standardized examination, no specific tests).
Liu et al (2002) Prenat Diagn 22 : 725-729.	Novel mutations and prenatal sonographic findings of glutaric aciduria (type I) in two Taiwanese families.	Study design: - Case report (*n*=3)	- Report on GCDH deficiency in three Taiwanese children, two of them showing dystonia - Prenatal ultrasound in one child (starting at age 30 weeks of gestation): progressive dilatation of the quadrigeminal cistern, macrocephaly, frontotemporal atrophy and enlarged Sylvian fissure. - Hypothesis that macrocephaly and frontotemporal atrophy developed following cytotoxic edema, cell damage and reduced CSF reabsorption (as previously suggested by Naidu and Moser 1991; Am J Neuroradiol 12: 413-416).
Lütcherath et al (2000) Acta Neurochir (Wien) 142 : 1025-1030	Children with bilateral temporal arachnoid cysts may have glutaric aciduria type 1 (GAT1); operation without knowing that may be harmful.	Study design: - Case report (n=2)	- Macrocephaly, bitemporal arachnoid cysts, subdural bleeding (one patient), delayed motor development - Neurosurgical interventions: fenestration, subduro-peritoneal and ventriculo-peritoneal shunts - Diagnosis of GA-I was made after the neurosurgical intervention both patients had a very poor outcome

			after neurosurgery (one patient died at 3 years of age, one had a severe motor handicap) - Conclusions: Children with bitemporal arachnoid cysts may have GA-I; all children with bitemporal cysts should be screened for GA-I before neurosurgical intervention
Martinez-Lage et al (1994) Childs Nerv Syst 10 : 198-203.	Macrocephaly, dystonia, and bilateral temporal arachnoid cysts : glutaric aciduria type 1.	Study design: - Case report (n=2)	- Macrocephaly, psychomotor delay, and progressive dystonia in two siblings - The initial diagnosis was of hydrocephalus and bilateral temporal cerebrospinal fluid collections. - VP shunting showed only modest neurological improvement. - Metabolic investigations confirmed GA-I - Conclusion: Macrocephaly, dystonia and bilateral temporal arachnoid cysts seems to be diagnostic of GA-I
Möller et al (2003). Neuropediatrics 34 : 57-60.	Investigation of the cerebral energy status in patients with glutaric aciduria type I by 31P magnetic resonance spectroscopy.	Study design: - Case report (n=2), phosphorus magnetic resonance spectroscopy	- No cerebral depletion of phosphocreatine (PCr) was observed. - Conclusion: a severe global and permanent depletion of cerebral energy supplies was ruled out. Creatine supplementation seems doubtful.
Morton et al (1991) Am J Med Genet 41:89-95. → see also: Bjugstad et al (2000); Strauss et al (2003)	A common cause of episodic encephalopathy an spastic paralysis in the Amish of Lancaster County, Pennsylvania	Study design: - Cohort study in 14 children from the Old Order Amish community in Lancaster County, Pennsylvania. → See Strauss et al 2003	**Clinical course of the disease** - Description of a remarkable clinical variation from acute infantile encephalopathy and sudden death to static extrapyramidal cerebral palsy. - 10/14 patients: Manifestation between age 3 to 18 months. Little progression of neurologic disorder after age 5 years in surviving children with sparing of intellect. - Deaths: 4 children in early childhood died during acute illnesses. **Treatment options** - Restriction of dietary protein, limitation of protein catabolism, dehydration, and acidosis during illnesses may prevent the onset of progression of neurologic disease. **Pedigree** - A pedigree chart tracing both parents of all except one case to John Lapp and his wife, who immigrated to the United States in 1730s, was presented.
Niiyama et al (2001) Eur J Dermatol 11: 244-246.	Acrodermatitis acidemica secondary to malnutrition in glutaric aciduria type I.	Study design: - Case report (*n*=1)	- First report on acrodermatitis acidemica in a child with GA-I - Severe deficiency of amino acids (in particular isoleucine), zinc, selenium, and variety of vitamins were found - Conclusion: Skin lesions were the result of severe malnutrition (like in methylmalonic and propionic acidurias).
Oguz et al (2005) Neuroradiology 47:229-234	Diffusion-weighted MR imaging and MR spectroscopy in glutaric aciduria type I.	Study design: - Case report (*n*=1), magnetic resonance spectroscopy (MRS) and diffusion-weighted MRI (DWI)	- DWI: Widespread restricted diffusion in the white matter and increased diffusion in bilateral putamen. - MRS: decreased N-acetyl-aspartate (NAA)/creatine (Cr) ratio; no significant change in choline (Cho)/Cr ratio. Increased lactate peak reflecting disturbed mitochondrial functions.
Prevett et al (1996) J Neurol Neurosurg Psychiatry 60 : 252-253. → see also: Bjugstad et al (2000)	Glutaric aciduria type I in adulthood.	Study design: - Case report (*n*=1)	- Suspected late-onset GCDH deficiency; diagnosis at age 50 years during reassessment of chronic neurological disability - Manifestation of gait disturbance and orofacial dyskinesia (first symptoms starting at age 7 years during an episode of “paralytic illness”) without previous acute encephalopathic crisis - MRI: Basal ganglia with abnormalities, focal areas of white matter changes.
Rakocevic et al (2004) Stereotact Funct	Bilateral pallidotomy for severe dystonia in an 18-month-old	Study design: - Case report (*n*=1) - 18-months-old male (Cherokee Indian)	- Partial improvement of dystonia and reduction of pain (only subjective estimation is given), “more alert and

Neurosurg 82: 80-83.	child with glutaric aciduria.	with severe generalized dystonia who underwent pallidotomy after pharmacological therapy (pharmacotherapy for movement disorders is not given in full detail, botulinum toxin A has been applied only with transient benefit).	interactive", no purposeful use of hands and arms. - Side effect: Pathological eye findings (right gaze preference, limitation of left horizontal gaze).
Seccombe et al (1986) Neurology 36: 264-267. → see also: Bjugstad et al (2000)	L-Carnitine treatment in glutaric aciduria type I.	Study design: - Case report (*n*=1) - 5-year-old girl (child of non-consangineous Yugoslavian parents), diagnosed at age 23 months after delayed motor development; treatment with protein restriction (1.1 g/kg/day), riboflavin (100 mg/day), and L-carnitine (3x500 mg/day)	**Biochemical response:** - Carnitine: Strong increase in free carnitine (normalization) and moderate increase in acylcarnitines in plasma. **Clinical response:** - Protein restriction and carnitine supplementation: no clinical improvement.
Smith et al (2001) Pediatrics 107: 1184-1187.	Glutaric academia, type I, missed by newborn screening in an infant with dystonia following promethazine administration.	Study design: - Case report (*n*=1)	- Case report on unsuccessful neonatal screening (cut-off problem; negative result at recall) - Child was diagnosed by diagnostic work-up of dystonia
Soffer et al (1992) J Neurol Sci 107:199-204. → see also: Bjugstad et al (2000)	Striatal degeneration and spongy myelinopathy in glutaric acidemia	Study design: - Case report and *post mortem* examination in one child (age 6.5 years) with fatal disease course. Review on 8 published *post mortem* cases.	**Clinical presentation and therapy** - Acute encephalopathic crisis at age 4 months, resulting in severe dystonia. Diagnosis was not made at age 15 months. Death occurred at age 6.5 months due to respiratory failure. - Treatment with lysine-restricted diet, riboflavin, carnitine, and baclofen without improvement of the neurological status. **Post mortem examination** **-** CNS: Increased brain weight, cerebral edema. Putamina were shrunken and pale, caudate nuclei were greatly attenuated. Histopathology revealed marked neuronal loss (surviving neurons were mainly of the large type) and prominent astrogliosis in striatum. Spongiform changes of the white matter were demonstrated throughout the brain.
Twomey et al (2003) Pediatr Radiol 33 : 823-830. → see also: Monavari and Naughten (2000); Naughten (2004)	Neuroimaging findings in glutaric aciduria type I.	Study design: - Retrospective evaluation of US, CCT and MRI scans in *n*=20 Irish patients	**Neuroradiological findings** - Widening of Sylvian fissures and of the fluid spaces anterior to the temporal lobes: 93% - Widening of mesencephalic cistern: 86% - Abormal high signal intensity in basal ganglia and periventricular white matter (T2): 64% - 9/14 patients with MRI scans had lesions in globus pallidum (in 4 cases isolated), putamen was abnormal in three patients but never isolated) - Abnormal high T2 signal were also found in the dentate nucleus (79%), substantia nigra (43%) and the pontine medial lemniscus (64%). - Four neonates followed with US showed bilateral multiple caudothalamic cysts. **Conclusion** Widening of Sylvian fissure, mesencephalic cistern and expansion of CSF spaces anterior to the temporal lobes are cardinal signs of GA-I. If combined with abnormalities of the basal ganglia and white matter abnormalities, GA-I should be strongly suspected.
Walter (2003) J Inherit Metab Dis 26: 181-188.	L-Carnitine in inborn errors of metabolism: What is the evidence?	Study design: - Questionnaire-based evaluation (via Metab-l) of current practice of oral L-carnitine supplementation in MCAD deficiency, propionic (PA) and methylmalonic acidurias (MMA); glutaric aciduria type I was only included into the discussion. - Literature review (PubMed): evaluation	**- Questionnaire:** Replies from 31 clinics in Europe, North America, Asia, and Australia: 94% of PA and MMA but only 39% of MCAD patients received L-carnitine (25-300 mg/kg/d orally) **- Literature review:** Most papers supported use of L-carnitine in PA and MMA, documenting biochemical or clinical improvement; only 5 relevant papers were

		of evidence levels according to SIGN	identified for MCAD deficiency. At best, studies could be ranked as 2+ (evidence from well-conducted case-cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal); majority are level 3 (evidence from non-analytical studies, e.g. case reports, case series). **- Conclusions:** Using SIGN criteria, recommendations for oral L-carnitine supplementation in these diseases would only be graded as D (lowest grade).
Woelfle et al (1996) Pediatr Radiol 26 : 779-781. → see also: Bjugstad et al (2000)	Subdural hematoma and glutaric aciduria type I.	Study design: - Case report (*n*=1)	- Bilateral subdural hemorrhages and frontotemporal atrophy; neurosurgical intervention; regression of subdural effusions but deterioration of neurologic disease - Diagnosis was just made after the neurosurgical intervention - Conclusion: GA I should be included into the differential diagnosis of unexplained subdural hematoma and neurological deficits

Level 4. Expert opinion

a) Reviews

Authors	Title	Description	Contents
Baric et al (1998) J Inherit Metab Dis 21 : 326-340.	Diagnosis and management of glutaric aciduria type I.	Review On diagnostic work-up and treatment in GCDH deficiency. Based on the presentations and discussions of the 2nd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Rauischholzhausen, Germany, 1996).	**Well-day treatment:** - Carnitine supplementation (30-100 mg/kg/d) ; - Co-factor responsiveness should be investigated but has found in only one patient (Chalmers, unpublished observation); - Benefit of long-term dietary treatment is unclear (lysine restriction until 6 y using AA mixtures and moderate protein restriction [1.5 g/kg/d] at age > 6 y) - Tryptophan-free AA mixtures should be avoided due to severe side effects (sleepliness, ill temper, irritability, loss of appetite, death) - Dystonia may worsen on high-protein meals et vice versa (anecdotal reports) **Emergency treatment:** a) Management at home: - Stop natural protein (not longer than 24 h) - Increase energy: 1.5 x basal requirements using carbohydrate drinks - Double carnitine dosage (200 mg/kg/d) b) Management at hospital: - See a) - IV Infusion of high-calorie glucose (if necessary with insulin) and lipids; - Sedation: Diazepam 0.25 mg/kg every 6 h; - IV carnitine (100-200 mg/kg/d); - Antipyretics; - Additional medication: riboflavin (100 mg/d), dextrometrophan (initial: 25 mg p.o., maintenance: 2.5 mg/kg every 12 h)
Hoffmann and Zschocke (1999) J Inherit Metab Dis 22: 381-391.	Glutaric aciduria type I: From clinical biochemical and molecular diversity to successful therapy.	Review: Based on the presentation at the 37th SSIEM meeting in York, UK (1998)	**Well-day treatment:** - Restriction of natural protein *plus* lysine-free AA mixtures - Carnitine supplementation **Emergency treatment:** - High-dose glucose and carnitine therapy **Monitoring:** - No statement
Kölker et al (2004) J Inherit Metab Dis 27: 893-902.	Emergency treatment in glutaryl-CoA dehydrogenase deficiency.	Review: Based on a presentation and the discussion at the 3rd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Heidelberg,	**Outpatient/home emergency treatment:** - Recommendations for maltodextran/dextrose, protein intake, and pharmacotherapy **Inpatient emergency treatment**

		Germany, 2003).	- Recommendations for energy requirements, protein intake and pharmacotherapy
Mühlhausen et al (2004) J Inherit Metab Dis: 885-892.	Maintenance treatment of glutaryl-CoA dehydrogenase deficiency.	Review: Based on a presentation and the discussion at the 3rd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Heidelberg, Germany, 2003).	Critical review on the state of art on dietary treatment, carnitine supplementation, riboflavin administration, and other treatment strategies (creatine, antioxidations) as well as on surgical interventions (pallidotomy) and monitoring.
Müller and Kölker (2004) J Inherit Metab Dis 27: 903-910.	Reduction of lysine intake while avoiding malnutrition – major goals and major problems in dietary treatment of glutaryl-CoA dehydrogenase deficiency	Review: Based on a presentation and the discussion at the 3rd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Heidelberg, Germany, 2003). Including: Calculations on essential amino acids, minerals and micronutrients as a basis for a well-balanced diet of this disease; discussion on age-dependent demands and pitfalls and a reasonable way to use international dietary recommendations.	**Major goals and major problems:** - To maintain normal growth and development by reducing production of (toxic) organic acids via reduction of lysine while avoiding malnutrition → two opposing goals; - Dietary recommendations for natural protein intake has many open questions: No recommendation for handicapped children; mixed vs standard protein; no exact data on intestinal uptake of AA mixtures; - Lysine content in natural protein is highly variable; - In general, dietary treatment can be performed either by protein-restricted or lysine-restricted diet; - **Protein restriction has two major disadvantages**: a) risk of malnutrition (AA and micronutrients), b) lysine intake cannot be controlled if protein sources are not standardized → AA mixtures decrease the risk for malnutrition, in particular during the vulnerable period for encephalopathic crises (risk for malnutrition is highest during the vulnerable period!). - A well-balanced dietary treatment cannot be adequately performed if intake of natural protein is the *only* parameter under control. - Dietary treatment is not possible without **regular monitoring** of amino acids, free carnitine, and micronutrients in plasma/serum
Prietsch V et al (2002) J Inherit Metab Dis 25: 531-546.	Emergency management of inherited metabolic diseases.	Review: Emergency management in different inborn errors of metabolism, also including "disorders of intoxication type" (this is not specific for GA-I but includes all organic acidurias, hyperammonemias etc).	Principles of emergency treatment for "intoxication type": - stop oral intake of toxic precursors (protein; not longer than 24-48 h, then introduce step-wise) - reversion of catabolism (glucose 10 mg/kg/min; ie approx. 60 kcal/kg/d) - specific detoxification measures (L-carnitine 100-300 mg/kg/d i.v.)
Superti-Furga and Hoffmann (1997) Eur J Pediatr 156: 821-828.	Glutaric aciduria type 1 (glutaryl-CoA dehydrogenase deficiency): advances and unanswered questions.	Review: Report from the 2nd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Rauischholzhausen, Germany, 1996)	**Carnitine supplementation:** - Lethal outcome in patients without carnitine supplementation; prevention of encephalopathic crises (see Hoffmann et al 1996); - Secondary carnitine depletion in nearly all patients before carnitine supplementation → **Carnitine supplementation is recommended.** Initial dosage: 100 mg/kg/d **Dietary treatment:** - No significant beneficial effect in lysine- and tryptophan-restricted patient (see Hoffmann et al 1996) - One patient died due to severe tryptophan depletion → **Lysine- and tryptophan-restricted diet is not recommended, moderate protein restriction is recommended.**
Yannicelli et al (1994) J Am Diet Assoc 94: 183-191.	Nutrition support for glutaric acidemia type I	Review: Case reports on lysine- and protein (*n*=14)-restricted patients (*n*=19); Reference to dietary recommendations	**Pharmacological treatment:** **a) Riboflavin**: most studies failed to show a positive effect; **b) VPA:** inconsistent results; secondary

		for protein and micronutrients	carnitine depletion as severe side effect; **c) Carnitine:** 100-300 mg/kg/d to normalize plasma levels of free carnitine. **Dietary treatment:** - Biochemical response if Lys intake is 70 mg/kg/d and Trp intake is 30 mg/kg/d; correlation between plasma Lys and plasma GA concentrations; - Poor growth and low plasma Lys and Trp concentration if intake further decreases (Lys < 50 mg/kg/d, Trp < 10 mg/kg/d); - Dietary treatment should not be discontinued, since the natural history of the disease is not yet known in the long run. **Guidelines for nutrition support:** **a) Well-day treatment** - Major goal: Promote normal growth and development (or prevent further neurologic deterioration) by lowering GA in plasma, CSF, and urine while maintaing normal plasma levels of Lys and Trp. - Intake of essential AA and micronutrients should meet or exceed 100% of RDAs (1989); - Lysine content in food is highly variable: protein foods in biologic value (meat, poultry, fish, eggs) is not recommended; - Energy supply may be higher in handicapped children; - Gastrostomy should be considered if feeding difficulties limit oral feeding; **b) Emergency treatment** - Major goal: Inhibit protein catabolism during acute illness; - Lys and Trp sources should be temporarily eliminated; - Low protein intake is necessary to avoid catabolism of muscle protein; - Energy: at least 120 % of recommended intake for age; - If oral feeding is not possible, glucose, lipids, and Lys/Trp-free solutions should be administered IV **c) Monitoring** - Anthropometrics - Iron status - Nutrient intake (3-day diet records) - Plasma carnitine status - GA: urine, plasma, (CSF) – initially: weekly, then: every 2 to 4 weeks - Lysine, tryptophan (plasma) – initially: weekly, then: every 2 to 4 weeks - Protein status - Trace minerals

b) Recommendations and textbooks

Authors	Title	Description	Contents / Recommendations
Hoffmann and Lehnert (2001)	„Organoacidopathien [C8]". In: Deutsche Gesellschaft für Kinderheilkunde und Jugendmedizin *"Leitlinien für Kinderheilkunde und Jugendmedizin"*. München: Urban & Fischer.	German S1 Guideline; General approach to organic acidurias; Specification of disease course, diagnosis and treatment in GA-I	**Well-day treatment:** - Protein restriction or lysine restriction using AA mixtures; - Carnitine supplementation; - Riboflavin (recommended only if sensitivity can be shown) **Emergency treatment:** - IV infusion with high doses of glucose and carnitine
Hoffmann (2000)	Disorders of lysine catabolism and related cerebral organic acid disorders. In: *Inborn Metabolic Disease,*	Description of clinical presentation, neuroradiologic findings, metabolic derangement, diagnostic tests, treatment and prognosis.	**Well-day treatment:** - Protein restriction or lysine restriction using AA mixtures; - Carnitine supplementation; - Riboflavin (recommended only if sensitivity can be shown)

	3rd edition. Fernandes, Saudubray, van den Berghe (eds). Springer: Berlin, Heidelberg, New York: 241-255.		**Emergency treatment:** Frequent feedings, high carbohydrate and zero protein intake, followed by high-dose intravenous glucose and carnitine, if necessary. Clomethiazole may be useful in severe cases of hyperpyrexia. **Neuropharmacological agents:** Baclofen or benzodiazepines have the effect for the treatment of dystonia. Limited information on other neuropharmacological agents. Valproic acid should not be administered.
Hoffmann, Müller, Szczerbak (1998)	Milupa broschure *"Glutaric aciduria type I"*	Based on Hoffmann et al (1991, 1996) and the 2nd European Workshop on Glutaryl-CoA dehydrognease deficiency; reference to general recommendations for daily intake of AA and micronutrients Practical guidance for pediatricians using lysine-free AA mixtures for diet	This broschure gives a precise description of lysine-restricted diet using lysine-free AA mixtures plus carnitine supplementation for well-day treatment, and implementation of emergency treatment during intercurrent illnesses. Contents: - Recommendations for intake of AA, lysine, tryptophan, energy, and carnitin; - Oral emergency treatment protocol - Emergency letter for patients - Examples for dietary management at different ages and tables for lysine content of nutrients etc.
Goodman and Frerman (2001)	Organic acidemias due to defects in lysine oxidation: 2-ketoadipic academia and glutaric academia. In: *The Metabolic & Molecular Basis of Inherited Disease, 3rd edition.* Scriver, Beaudet, Valle, Sly (eds). McGraw-Hill: New-York: 2195-2204.	Description of clinical presentation, neuroradiologic findings, anatomic pathology, molecular basis of disease, pathogenesis, genetics, incidence, diagnosis and screening, prenatal diagnosis, and treatment.	**Well-day treatment:** - The role of dietary treatment is not clear but may be beneficial; - Carnitine supplementation is recommended; **Emergency treatment:** Is important to prevent acute encephalopathic crises: fluids, insulin, and glucose (no exact protocol is given) **Neuropharmacological agents:** Baclofen and vigabatrin may be helpful, valproic acid – although theoretically beneficial – should be avoided.
Zschocke and Hoffmann (2004)	"Cerebral" organic acidurias. In: *Vademecum Metabolicum, 2nd edition.* Zschocke, Hoffmann (eds). Schattauer: 67.	Short description of clinical phenotype, enzyme, diagnosis, differential diagnosis, and therapy	Strict adherence to emergency protocol in infancy and early childhood. Carnitine 100 mg/kg/day, diet (Lys- and Trp-restricted, beware of Trp deficiency!).

Abbreviations

ADC	Apparent diffusion coefficient
APS	Arbeitsgemeinschaft für angeborene Stoffwechselstörungen
ASIEM	Australasian Society for Inborn Errors of Metabolism
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BT-A	Botulinum toxin A
C5DC	Glutarylcarnitine
CART	Classification-and-regression-tree
CNS	Central nervous system
CCT	Cranial computer tomography
CSF	Cerebrospinal fluid
DBS	Dried blood spots
EPI-SE MRI	Diffusion-weighted MRI
GA	Glutaric acid
GCDH	Glutaryl-CoA dehydrogenase
GC/MS	Gas chromatography/mass spectrometry
JSIEM	Japanese Society for Inborn Errors of Metabolism
MRI	Magnetic resonance imaging
MS/MS	Tandem mass spectrometry
3-OH-GA	3-Hydroxyglutaric acid
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Society for Inherited Metabolic Disorders
SSIEM	Society for the Study on Inborn Errors of Metabolism

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