J Inherit Metab Dis (2007) 30:5–22
DOI 10.1007/s10545-006-0451-4

GUIDELINE

Guideline for the diagnosis and management of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type I)

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Received: 17 August 2006 / Submitted in revised form: 30 November 2006 / Accepted: 1 December 2006 / Published online: 3 January 2007

Communicating editor: Rodney Pollitt

Competing interests: A statement of competing interests is provided in the electronic supplementary material available online.

Contributions of authors: Full details are provided in the electronic supplementary material available online.

References to electronic databases:
Glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type I): OMIM # 231670
Glutaryl-CoA dehydrogenase: EC 1.3.99.7

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Electronic Supplementary Material
Supplementary material is available for this article at http://dx.doi.org/10.1007/s10545-006-0451-4

Summary Glutaryl-CoA dehydrogenase (GCDH) deficiency is an autosomal recessive disease with an estimated overall prevalence of 1 in 100 000 newborns. Biochemically, the disease is characterized by accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and glutarylcarnitine, which can be detected by gas chromatography–mass spectrometry of organic acids or tandem mass spectrometry of acylcarnitines. Clinically, the disease course is usually determined by acute encephalopathic crises precipitated by infectious diseases, immunizations, and surgery during infancy or childhood. The characteristic neurological sequel is acute striatal injury and, subsequently, dystonia. During the last three decades attempts have been made to establish and optimize therapy for GCDH deficiency. Maintenance treatment consisting of a diet combined with oral supplementation of L-carnitine, and an intensified emergency treatment during acute episodes of intercurrent illness have been applied to the majority of patients. This treatment strategy has significantly reduced the frequency of acute encephalopathic crises in early-diagnosed patients. Therefore, GCDH deficiency is now considered to be a treatable condition. However, significant differences exist in the diagnostic procedure and management of affected patients so that there is a wide variation of the outcome, in particular of pre-symptomatically diagnosed patients. At this time of rapid expansion of neonatal screening for GCDH deficiency, the major aim of this guideline is to re-assess the common practice and to formulate recommendations for diagnosis and management of GCDH deficiency based on the best available evidence.

Abbreviations

3-OH-GA	3-hydroxyglutaric acid
AA	amino acid(s)
ADC	apparent diffusion coefficient
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BT-A	botulinum toxin A
C5DC	glutarylcarnitine
CCT	cranial computed tomography
DBS	dried blood spots
EPI-SE	echo-planar imaging spin-echo
GA	glutaric acid
GCDH	glutaryl-CoA dehydrogenase
GCP	good clinical practice
GC-MS	gas chromatography–mass spectrometry
GDG	guideline developmental group
HPLC	high-performance liquid chromatography
Lys	lysine
MR	magnetic resonance
MRI	magnetic resonance imaging
MS/MS	tandem mass spectrometry
SIGN	Scottish Intercollegiate Guidelines Network
TE	echo time
TR	repetition time
Trp	tryptophan

Introduction

Glutaryl-CoA dehydrogenase (GCDH, EC 1.3.99.7) deficiency (synonym, glutaric acidaemia or aciduria type I) is an autosomal recessive disease that was first described in 1975 (Goodman et al 1975) and has an estimated overall prevalence of 1 in 100,000 newborns (Lindner et al 2004). The *GCDH* gene is localized on chromosome 19p13.2 and encodes a flavin–adenine dinucleotide-dependent mitochondrial matrix protein that is involved in the catabolism of L-lysine, L-hydroxylysine and L-tryptophan (Fu et al 2004; Greenberg et al 1995). More than 150 disease-causing mutations are known (Goodman et al 1998; Zschocke et al 2000). Biochemically, GCDH deficiency is characterized by an accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid (less frequently), and glutarylcarnitine (C5DC). These can be detected in body fluids (urine, plasma, CSF) and tissues by gas chromatography–mass spectrometry (GC-MS; Baric et al 1999) of organic acids or by electrospray-ionization tandem mass spectrometry of acylcarnitines (MS/MS; Chace et al 2003). Two biochemically defined subgroups of patients are distinguished, based on urinary metabolite excretion of GA, i.e. *low* excretors (GA $<$ 100 mmol/mol creatinine) and *high* excretors (GA $>$ 100 mmol/mol creatinine), both of them presenting with the same but variable clinical phenotype (Baric et al 1999; Busquets et al 2000; Christensen et al 2004; Kölker et al 2006).

Since the description of the two index patients in 1975 (Goodman et al 1975), more than 400 patients have been identified worldwide. Three genetic isolates with a high carrier frequency (up to 1:10) and over-representation of this disease have been identified, including the Amish Community (Morton et al 1991), Canadian Oji-Cree Indians (Haworth et al 1991), and the Irish Travellers (Naughten et al 2004). Untreated, most patients will develop neurological disease during a finite period of brain development (age 3–36 months) following an encephalitis-like, acute encephalopathic crisis often precipitated by febrile illness, immunization, or surgical intervention (Hoffmann et al 1991; Kölker et al 2006). The characteristic neurological sequel of these crises is acute bilateral striatal injury and, subsequently, a movement disorder. Dystonia is the dominant extrapyramidal symptom, often accompanied by spasticity (Hoffmann et al 1991; Kyllerman et al 1994). Morbidity and mortality are high in patients who have had a crisis (Kölker et al 2006; Kyllerman et al 2004). In a few patients, neurological disease has been demonstrated in the absence of any documented

encephalopathic crisis and has been termed *insidious-onset* type (Busquets et al 2000; Hoffmann et al 1996) and *late-onset* type (Bähr et al 2002; Kulkens et al 2005).

During the last three decades attempts have been made to establish and optimize therapy for GCDH deficiency. Dietary treatment 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 considerably reduced the frequency of acute encephalopathic crises and thus morbidity and mortality in early-diagnosed patients (Kölker et al 2006; Monavari and Naughten 2000; Strauss et al 2003). Therefore, GCDH deficiency should now be considered to be a treatable condition.

Early clinical diagnosis is hampered by the lack of a characteristic or even pathognomonic signs and symptoms before an encephalopathic crisis. Macrocephaly is found in approximately 75% of patients during infancy (Bjugstad et al 2000; Kölker et al 2006), but is non-specific. Therefore, GCDH deficiency has been included in some expanded MS/MS-based neonatal screening programmes (e.g. Germany, Australia, Qatar, parts of USA). DNA-based mutation analysis is used for the high-risk screening in one cohort of low excretors (Greenberg et al 2002).

Significant differences exist in the diagnostic procedure and management of affected patients and there is a wide variation in the outcome, in particular of pre-symptomatically diagnosed patients (Kölker et al 2006). At this time of rapid expansion of neonatal screening for GCDH deficiency, the major aim of this guideline is to re-assess the common practice and to formulate recommendations for diagnosis and management of GCDH deficiency based on the best evidence available.

Methods

Guideline development

The guideline development process was initiated following the *3rd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency* in Heidelberg, Germany (October 2003). Three further meetings were held in Rimini (May 2004), Amsterdam (August 2004), and Prague (May 2005). The guideline developmental group (GDG) consists of paediatric metabolic specialists (A. B. Burlina, S. I. Goodman, C. R. Greenberg, G. F. Hoffmann, D. M. Koeller, S. Kölker [chairman], E. R. Naughten), clinical biochemists (E. Christensen, M. Duran, J. G. Okun [secretary]), a psychologist (P. Burgard), a specialist metabolic dietitian (E. Müller), a neurologist (A. P. Burlina), and a neuroradiologist (E. Neumaier-Probst). Working groups were established focusing on the guideline topics. The GDG members performed systematic literature review, drafted the guideline, and discussed it with the GDG members and external consultants. The guideline draft was reviewed by external consultants (J. V. Leonard, M. Dixon, M. Kyllerman, R. A. Surtees, B. Wilcken), and revisions were made by the GDG based on these comments. The revised guideline was sent to national and international societies for inborn errors for metabolism asking for endorsement. Thus far, the guideline has been endorsed by *Arbeitsgemeinschaft Pädiatrische Stoffwechselstörungen* (Germany), *Verenigung Erfelijke Stofwisselingsziekten Nederland* (The Netherlands), *Società Italiana per lo Studio delle Malattie Metaboliche* (Italy), and *Sociedade Portuguesa de Doenças Metabólicas* (Portugal).

Systematic literature review

The evidence base for this guideline was similar to the methodology used by SIGN (Scottish Intercollegiate Guideline Network; URL: http://www.sign.ac.uk). A systematic review of the literature on GCDH deficiency was carried out using Medline, Embase, the Cochrane Library, MedLink, and Orphanet. The years covered were 1975–2005. Internet searches were also performed on various websites including international and national societies for inborn errors of metabolism and those of parent groups. The main searches were selected and evaluated by a minimum of two members of the GDG before conclusions were considered as evidence (Suppl. Tables 1–4).

International cross-sectional study

In parallel with the systematic literature review, the GDG performed an international cross-sectional study on GCDH deficiency enrolling 279 patients from 35 international metabolic centres (Kölker et al 2006). This is the most comprehensive study on the natural history, outcome and treatment efficacy of this disease and thus is an important source of evidence for this guideline. To improve the level of evidence for important aspects of diagnosis and management in GCDH deficiency, a prospective follow-up study of newly diagnosed patients was started in 2002 (URL: http://www.metabnet.de). Its results will be an important basis for the revision of the guideline which is planned for 2009.

Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards 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

guideline recommendations will not ensure the correct diagnosis and satisfactory outcome in every case, nor should they be construed as including all proper methods 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 discussion of the options with the patient and his/her family, covering the diagnostic and treatment choices available.

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

Correct classification and differential diagnoses

GCDH deficiency (glutaric aciduria type I) is defined as inherited deficiency of GCDH confirmed by enzyme analysis and/or demonstration of two disease-causing mutations. All other signs, symptoms and laboratory abnormalities that are found in affected patients are not pathognomonic so that the diagnosis should be suspected, but not confirmed. These include macrocephaly, acute encephalopathy, basal ganglia injury, leukoencephalopathy, movement disorders, subdural and retinal haemorrhage, and increased urinary excretion of GA and 3-OH-GA as well as accumulation of C5DC. All of these have a wide differential diagnosis.

Statement #1 (Good clinical practice [GCP])
The correct classification of GCDH deficiency has important practical implications when devising individual treatment plans and giving appropriate information to children and their families. The diagnostic work-up should be done by metabolic specialists.

Neonatal and high-risk screening

Major aims: Timely diagnosis and start of treatment, i.e. before an acute encephalopathic crisis, is likely to result in a better outcome than diagnosis and start of treatment after the onset of neurological disease (Hoffmann et al 1996; Kölker et al 2006; Naughten et al 2004; Strauss et al 2003). The aim of neonatal and high-risk screening is to reduce the *a priori* risk for an acute encephalopathic crisis.

Definitions: MS/MS-based *neonatal* mass screening for GCDH deficiency is performed within the routine neonatal screening or expanded neonatal screening programmes and includes all newborns with a standard *a priori* risk for GCDH deficiency. *High-risk* screening for GCDH deficiency is performed in neonates with an increased *a priori* risk for GCDH deficiency.

MS/MS: Summarizing results from international screening laboratories, the overall prevalence of GCDH deficiency is approximately 1 in 100 000 newborns but varies considerably in different countries (Suppl. Table 5). The diagnostic test is C5DC in dried blood spots (DBS). In addition, some laboratories are also using ratios to other measured acylcarnitines and others repeat the analysis on another bloodspot from the same DBS as an internal quality control, but this is considered a matter for individual laboratories and no recommendations are given in these guidelines.

Cut-off levels: A C5DC value above the cut-off value is considered a positive case. The cut-off level for C5DC has to be set by each laboratory as it will be influenced by many factors (Suppl. Table 6). Cut-off levels are typically adjusted with more experience of screening, a process that is likely to continue. At present, there is no general recommendation for the establishment and setting of cut-off levels.

Diagnostic pitfalls: Probably not all patients, however, can be diagnosed by this method, as there are patients with a normal or only slightly increased C5DC concentration in DBS. Some patients with GCDH deficiency have been missed by newborn screening (Smith et al 2001; Wilcken et al 2003) or by retrospective analysis of the newborn blood spots (Gallagher et al 2005; Treacy et al 2003), particularly those with a low-excreting phenotype. Apparent increases in C5DC have been demonstrated in medium-chain acyl-CoA dehydrogenase deficiency, most probably because of acylcarnitines of identical mass, such as hydroxydecanoylcarnitine (Napolitano et al 2004). In patients with multiple acyl-CoA dehydrogenase deficiency, C5DC can also be elevated but is accompanied by increased concentrations of other acylcarnitines. Nowadays, most laboratories are using additional tests for follow-up investigations of initially positive screening results, such as analysis of urinary GA and 3-OH-GA.

Statement #2 (GCP)
For neonatal screening for GCDH deficiency, MS/MS should be used to detect C5DC in DBS.

Alternative methods for high-risk screening: Clusters of affected patients from genetic isolates with high carrier frequencies have been identified. The Amish and Irish Travellers have a high-excretor phenotype (Strauss et al 2003; Naughten et al 2004), whereas the Oji-Cree are low excretors (Greenberg et al 2002). High-risk screening in the Amish and the Irish Travellers was first performed by organic acid analysis, but detection of C5DC in DBS is now used. There have been no documented false negatives in the Amish and the Irish Traveller populations, whereas false negatives in the Oji-Cree were common when MS/MS was used (Greenberg,

personal communication, 2006). As a consequence, high-risk screening using a DNA-based technique on DBS has been implemented (Greenberg et al 2002).

Statement #3 (GCP)
In low excretors, screening by MS/MS may produce false-negative results. Thus, in a cohort with a high carrier frequency for a *GCDH* gene, mutation associated with low excretion DNA-based screening should be considered.

Confirmation of a positive screening result

A positive screening result should be confirmed by alternative techniques, including determination of GA and 3-OH-GA in urine by GC-MS, and finally mutation analysis in the *GCDH* gene and/or GCDH enzyme analysis (Baric et al 1999; Christensen 1983; Goodman et al 1998). 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. Normal 3-OH-GA excretion is likely to exclude the diagnosis, whereas elevated urinary excretion of 3-OH-GA should be followed by mutation analysis and start of treatment. In addition, unclear results of quantitative 3-OH-GA or the occurrence of clinical and neuroradiological abnormalities, which increase the *a priori* risk for GCDH deficiency (even if 3-OH-GA concentrations are normal), should also entail mutation analysis and start of treatment. The finding of two known disease-causing mutations will establish the diagnosis. If only one known disease-causing mutation or no mutations are found, GCDH enzyme activity should be determined. Low enzyme activity will again establish the diagnosis of GCDH deficiency, while normal activity will exclude the diagnosis (see Fig. 1).

Statement #4 (GCP)
For the confirmation of a positive neonatal screening result, a specific diagnostic work-up is required, including a quantitative analysis of GA and 3-OH-GA in urine, mutation analysis, and enzyme analysis.

Selective screening

Pre-test probability: If neonatal or high-risk screening programmes are non-existent, the diagnosis of GCDH deficiency should be made by selective screening. The major disadvantages of this approach is that there is no single clinical pathognomonic sign or symptom in GCDH deficiency that will reliably identify GCDH deficiency *before* an acute encephalopathic crisis. Only a few patients have been diagnosed pre-symptomatically in the course of diagnostic work-up of macrocephaly (Kölker et al 2006), which is non-specific per se. However, if it is combined with other clinical and neuroradiological signs (Suppl. Table 7), the probability for GCDH deficiency increases (Suppl. Table 8).

Methods: If there is clinical or neuroradiological suspicion (Suppl. Tables 7, 8), selective screening for GCDH deficiency should be done. In this section, we comment on the most frequently used methods and summarize best practice based on the clinical experience of the GDG. Detection of C5DC in DBS or plasma is useful for selective screening. If free carnitine is low, a single oral loading with 100 mg/kg carnitine will increase the production of C5DC, which can be analysed. However, there may be false-negative results in patients with a mild biochemical phenotype (low excretors). By contrast, C5DC concentrations in urine may be still elevated even with secondary carnitine depletion and also in low excretors (Tortorelli et al 2005).

Affected patients will excrete varying amounts of GA, 3-OH-GA, and – inconsistently – glutaconic acid (Baric et al 1999). Each laboratory should establish its own reference values. Whereas GA is excreted in large amounts in *high excretors*, it may be (near) normal in *low excretors* (Christensen et al 2004). The separation of 3-OH-GA from 2-hydroxyglutaric acid may be cumbersome. Mass-selective detection should always be performed. The diagnostic relevance of glutaconic acid is limited. Since quantitative organic acid analysis has some advantages for selective screening compared with MS/MS in DBS, i.e. higher sensitivity and specificity particularly in patients with secondary carnitine depletion, this is usually the first-line method for selective screening. False-positive test results have been observed for some other metabolic diseases and conditions (Suppl. Table 9).

Analysis of GCDH enzyme activity in fibroblasts or leukocytes is the 'gold standard' for confirming the diagnosis with a sensitivity of 100% (Christensen 1983; Christensen et al 2004; Kölker et al 2006). GCDH deficiency varies considerably, ranging from complete loss of GCDH activity in most patients up to nearly heterozygous values, i.e. 30% residual activity in some patients (Christensen et al 2004; Mühlhausen et al 2003).

Mutation analysis of the *GCDH* gene has a sensitivity of 98–99% (Zschocke et al 2000).

The use of *in vivo* loading tests using lysine or prolonged fasting tests is not recommended as the tests are potentially harmful and age-matched controls are usually not available. They should not be used for selective screening of GCDH deficiency. Alternatively, loading tests can be performed safely *in vitro* (Schulze-Bergkamen et al 2005), but there is no evidence that these are necessary for the confirmation of diagnosis.

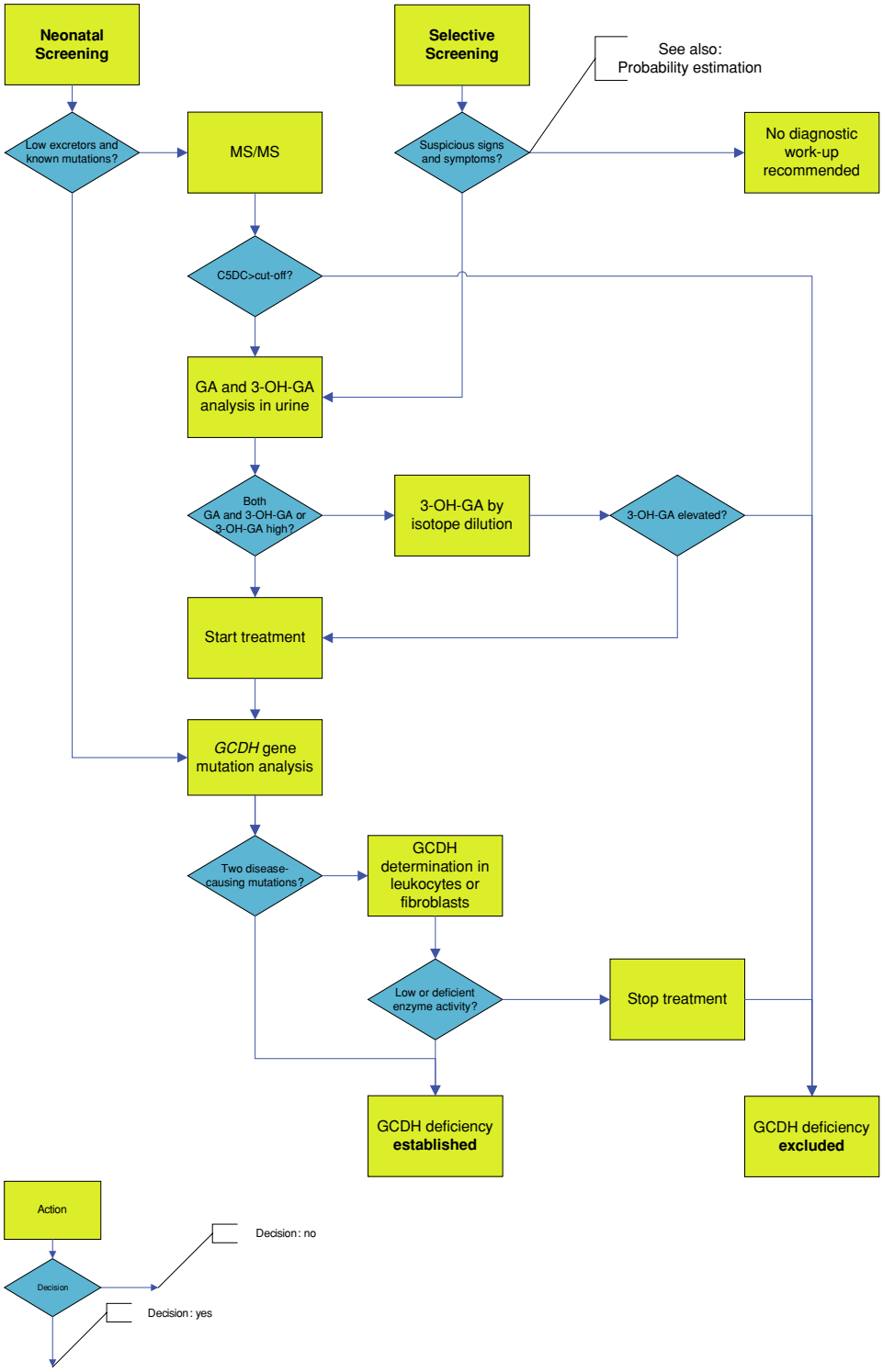

Fig. 1 Neonatal and selective screening, and confirmation of diagnosis. In general, neonatal and high-risk neonatal screening for GCDH deficiency is performed using MS/MS. For high-risk neonatal screening, a mechanism for the flagging of Guthrie cards of high-risk neonates should be established in screening 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 based on clinical and neuroradiological findings, see Suppl. Table 8

Statement #5 (GCP)
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 GA and 3-OH-GA in urine, *GCDH* gene mutation analysis, and/or enzyme analysis.

Figure 1 summarizes the diagnostic procedure for neonatal, high-risk and selective

screening, and confirmation of diagnosis in GCDH deficiency.

Metabolic maintenance treatment

Statement #6 (GCP)
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 cope successfully with these problems, dietary treatment and pharmacotherapy should be implemented by an interdisciplinary team including metabolic paediatricians, dietitians, nurses and occupational therapists. Parents and patients should have regular training including written information on dietary treatment to minimize the risk of dietary mistakes.

Treatment and outcome

Whereas the outcome in GCDH deficiency is poor in patients who have been diagnosed *after* acute encephalopathic crises (Bjugstad et al 2000; Busquets et al 2000; Hoffmann et al 1996; Kyllerman et al 2004), most patients remain clinically asymptomatic if diagnosed and treated *before* these crises (Kölker et al 2006; Naughten et al 2004; Strauss et al 2003). Although some pre-symptomatically diagnosed patients have still developed neurological complications, the value of early diagnosis and treatment is now undisputed. Since dietary treatment is used in combination with carnitine, riboflavin, and emergency treatment in the majority of children, the relative efficacy of each single component is not known. However, a recent international cross-sectional study has demonstrated a beneficial effect for lysine restriction and carnitine supplementation for maintenance treatment but not for protein restriction or riboflavin (Kölker et al 2006).

The value of dietary treatment is unclear in patients who already have neurological symptoms, but some patients may benefit by prevention of further encephalopathic crises or progression of neurological deterioration (Bjugstad et al 2000; Hoffmann et al 1996; Kölker et al 2006; Strauss et al 2003). Carnitine supplementation prevents secondary carnitine depletion and may partially improve or stop the progression of neurological disease, and reduce the mortality (Bjugstad et al 2000; Kölker et al 2006).

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 putatively toxic organic acids by restricting the intake of lysine (Lys) and tryptophan (Trp) while 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.

Dietary treatment

International dietary recommendations: International dietary recommendations have been developed by different international organizations outlining the age-dependent needs of the growing child (Suppl. Tables 10, 11). These recommendations also form the basis for dietary treatment in GCDH deficiency.

Statement #7 (GCP)
Any dietary treatment in GCDH deficiency that does not fulfil the international dietary recommendations is not recommended and should be considered as potentially dangerous.

Individualization of dietary treatment: To ensure that the majority of children obtain sufficient nutrients, international dietary guidelines for protein intake are usually set to be the mean plus 2 standard deviations. For some children a protein intake that is less than the 'safe intake' may be adequate for growth. However, symptomatic children with GCDH deficiency in particular may have increased requirements for nutrients and energy and an impaired intake. By contrast the loss of mobility decreases the energy demand (Müller and Kölker 2004; Yannicelli et al 1994). It is not known whether dietary recommendations will meet these varying demands. For these reasons, to achieve normal growth and development dietary treatment should take account of these guidelines but adjust to the individual's specific requirements.

Lysine restriction versus protein restriction: To reduce the production of GA and 3-OH-GA, dietary treatments have been developed to reduce the intake of the relevant precursors, in particular Lys restriction. At present, two strategies exist: *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 (Müller and Kölker 2004; Yannicelli et al 1994). The major difference between the two diets is that the Lys-restricted diet is calculated primarily via an estimation of daily Lys intake, whereas the protein-restricted diet is based on calculation of natural protein alone. Furthermore, Lys-restricted patients are usually supplemented with Lys-free, Trp-reduced amino acid (AA) mixtures. Lys- and protein-restricted diets have been used

for more than 10 years worldwide. Here, we will focus on Lys-restricted diet for the following reasons. (1) Basic principle: an estimation of daily Lys intake can be achieved more exactly using a calculation of Lys instead of protein (Suppl. Tables 10–12). (2) Outcome: the frequency of acute encephalopathic crises is lower in pre-symptomatically diagnosed patients treated with Lys-restricted than with protein-restricted diet (Kölker et al 2006).

Statement #8 (Recommendation grade C)
Lys-restricted dietary treatment (i.e. restriction of Lys to minimum requirements *plus* supplementation with Lys-free, Trp-reduced AA mixtures) is recommended for the metabolic maintenance treatment of GCDH deficiency, particularly in pre-symptomatically diagnosed patients up to 6 years of age.

Lysine restriction versus tryptophan restriction: Lys has become the major target for dietary treatment for the following reasons. (1) Natural protein consists of 2–9% Lys (Suppl. Table 12) but contains only 0.6–2% Trp, and thus Lys is the major source for GA and 3-OH-GA. (2) At present, accurate determination of plasma Trp, which is protein bound, is often not available and, therefore, is often not easily and reproducibly incorporated in the follow-up of patients. (3) Restriction of Trp intake can induce neurological dysfunction (secondary depletion of serotonin), such as insomnia, irritability, depression and disturbance of temperature regulation, and pellagra (secondary depletion of nicotinic acid). Trp depletion was thought to be associated with the death of one child (Hoffmann et al 1991), although there is no definite proof of a causal link.

AA supplements: Lys-free AA supplements, containing all essential AA (except for Lys) and usually (but not in all products!) minerals, trace minerals and vitamins, are an integral part of dietary treatment. Following the manifestation of acute encephalopathic crises, feeding and gastrointestinal problems are frequently found, including problems with chewing and swallowing, vomiting, gastro-oesophageal reflux, and diarrhoea (Bjugstad et al 2000; Kölker et al 2006; Kyllerman et al 2004; Strauss et al 2003). The taste and acidity of AA mixtures may add to previous gastrointestinal problems and a stepwise increase in AA mixtures may be necessary.

Statement #9 (GCP)
Lys-free AA supplements, preferably reduced in Trp and supplemented with vitamins, minerals and trace minerals, should be used for dietary treatment.

Dietary treatment after the age of 6 years: The long-term outcome in patients with GCDH deficiency has not been well documented. Besides the acute encephalopathic crises, there is also evidence of chronic neurological deterioration in patient subgroups with no documented crisis, i.e. the late-onset and insidious-onset types (Bähr et al 2002; Busquets et al 2000; Hoffmann et al 1996; Külkens et al 2005). The benefit of dietary treatment after age 6 years has not yet been precisely determined. However, single case reports have suggested a potential benefit; therefore, it may be advisable to continue dietary treatment but using a less strict protocol than before age 6 years.

Statement #10 (GCP)
Dietary treatment after age 6 years

- Avoid excessive intake of natural protein (protein intake according to Dewey et al 1996).
- 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: Following acute encephalopathic crises, many children suffer from severe feeding problems and have increased energy demand due to the movement disorder. These children are at increased risk for malnutrition if dietary management does not consider their requirements (Müller and Kölker 2004; Yannicelli et al 1994). In general, mobility and feedings skills are important prognostic parameters (Kölker et al 2006). It is important to be aware that energy requirements may also be markedly reduced as some patients are not mobile. Although the individual approach to coping with these feedings problems may differ, there are some general recommendations that it is helpful to consider.

Statement #11 (GCP)
Management of feeding problems

1. General recommendations

   - Monitor growth and intake of essential nutrients.
   - Keep the head in the midline position in dystonic patients.
   - Consider tube and overnight feeding.

2. Children with mild to moderate feeding problems

   - Use semi-solid food with low Lys content; enrich food with protein-free formula powder (including micronutrients) or use maltodextrin, cream and/or vegetable oil. Alternatively, protein-free high-energy drinks can be administered as nutritional supplements.
   - Increase the frequency of meals and reduce the quantity in each.

3. Children with severe feedings problems

   - Intensify the management (see 2); introduce gastrostomy feeding.

- Reduce the volume of solid food (by increasing the concentration); concomitantly increase the quantity of fluids. Solid food and fluids should be served separately.
- Implement a late meal.

4. Children with severe vomiting

- See (2)
- Consider pharmacotherapy.
- Consider fundoplication, gastrostomy, or jejunostomy.

Training: In addition to exact calculation of dietary treatment as outlined above, the efficacy of dietary treatment depends critically on adequate information and education of parents and patients. Implementation of this requires the expertise of a metabolic dietitian who can provide regular training and provision of good resources, thus enabling the diet to be easily managed at home.

Pharmacotherapy

Carnitine supplementation: Secondary carnitine depletion is common in untreated patients (Hoffmann et al 1996; Lipkin et al 1988; Seccombe et al 1986). Conjugation of glutaryl-CoA is considered a physiological detoxification to form non-toxic C5DC and to replenish the intracellular CoA pool (Seccombe et al 1986). L-Carnitine supplementation is thought to improve the outcome in the majority of patients with GCDH deficiency (Hoffmann et al 1996; Kölker et al 2006; Strauss et al 2003). No severe adverse events, such as sudden deaths, arrhythmias or rhabdomyolysis have been reported for L-carnitine supplementation in GCDH deficiency.

Statement #12 (Recommendation grade C)
L-Carnitine should be supplemented in all patients with GCDH deficiency and should be continued lifelong.

Statement #13 (GCP)
To prevent or reverse secondary carnitine depletion, an initial dosage of 100 mg L-carnitine/kg per day 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 per day p.o. in children (>6 years). A reduction of L-carnitine should be considered carefully if side-effects, such as diarrhoea and fish odour, occur.

Riboflavin: Although an improvement of biochemical parameters has been suggested in single patients (Brandt et al 1979; Lipkin et al 1988), there is no firm evidence that riboflavin improves the neurological outcome of this disease (Kölker et al 2006). Riboflavin responsiveness in GCDH deficiency appears to be rare (Chalmers et al 2006).

Statement #14 (Recommendation grade C)
Riboflavin should be administered only if riboflavin responsiveness has been proved.

Neuroprotective agents: There is no firm evidence that administration of other drugs, such as phenobarbital, *N*-acetylcysteine, creatine monohydrate, topiramate, glutamate receptor antagonists and antioxidants are beneficial for these patients (Greenberg et al 2002; Kyllerman et al 1994; Kyllerman et al 2004; Strauss et al 2003), although theoretically they may appear to be of value. In contrast, some of these drugs have a high frequency of adverse effects.

Statement #15 (Recommendation grade D)
Drugs with unproven neuroprotective effect for GCDH deficiency (e.g. antiepileptic drugs, glutamate receptor antagonists, creatine monohydrate, antioxidants) should not be used for the routine 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.

Emergency treatment

Acute encephalopathic crises

Routine treatment does not protect against encephalopathic crises, so it is necessary to use an intensified emergency treatment when the patient is thought to be at risk. However, there is a continuum between the onset of an intercurrent illness and the first signs of the neurological complications, so that it can be difficult to decide on therapy (Hoffmann et al 1996; Strauss et al 2003). A detailed description of encephalopathic crises is given in Suppl. Text 1.

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 (Hoffmann et al 1996; Monavari and Naughten 2000; Strauss et al 2003). Emergency treatment follows the basic treatment principles of metabolic diseases of the *intoxication type* (Dixon and Leonard 1992; Prietsch et al 2002). The following principles form the basis of emergency treatment protocols worldwide.

Statement #16 (Recommendation grade D)
The following principles should be used for emergency treatment:

Table 1 Metabolic maintenance treatment. Consider an individualization of treatment if normal growth and development is not achieved

Treatment		Age				
		0–6 months	7–12 months	1–3 years	4–6 years	>6 years
1. Lys-restricted diet						
Lys	mg/kg	100[a]	90[a]	80–60[a]	60–50[a]	Avoid excessive intake of natural protein; intake of natural protein with a low Lys content according to 'safe' values (Dewey et al 1996)
Trp	mg/kg	20[a]	17[a]	17–13[a]	13[a]	
Protein (natural)[b]	g/kg	1.4–1.3	1.5–1.3	1.4–1.3	1.3–1.1	
Protein (AA mixtures)	g/kg	1.3–0.8	1.0–0.8	0.8	0.8	
Protein (total)[b]	g/kg	2.7–2.1	2.5–2.1	2.2–2.1	2.1–1.9	
Energy[c]	kcal/kg	115–82	95–80	95–82	90–78	
2. Micronutrients[c]	%	≥100	≥100	≥100	≥100	>100
3. Pharmacotherapy						
Carnitine	mg/kg	100	100	100	100–50	30–50

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

[b]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 only protein restriction is instituted (i.e. *without* administration of Lys-free AA mixtures), intake of natural protein should be adjusted according to 'safe' values of international recommendations (Dewey et al 1996). 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, i.e. natural protein with *low* biological value

[c]According to international dietary recommendations. Energy demand may vary in different climatic zones

- Reverse catabolic state by administration of high-energy intake (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 physiological detoxifying mechanisms by carnitine supplementation and alkalinization of urine.
- Prevent secondary carnitine depletion by carnitine supplementation.
- Balance body fluids and pH state by rehydration and buffering.

Management of emergency treatment

Preventive care: Delay in starting the emergency regimen can have serious consequences and causes of a delay to start emergency treatment are many and varied, including inadequate training of parents and logistical problems. All of these should be identified systematically. Suppl. Table 13 summarizes helpful strategies to prevent hazardous delays in the start of emergency treatment.

Start of emergency treatment: The possibility of a crisis should be suspected during *each* putatively threatening episode during the vulnerable period (age 0–6 years). In particular, conditions accelerating catabolic state, such as repeated vomiting and diarrhoea (also in the absence of fever!), 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 (Bjugstad et al 2000; Hoffmann et al 1996; Kölker et al 2006; Strauss et al 2003). This may be in part due to increased resistance to catabolic state, but also the fact that there is a vulnerable period in these patients. Emergency treatment should aim to start *before* the onset of alarming neurological symptoms. The decision to institute emergency treatment should be made very freely with a low index of suspicion.

Statement #17 (Recommendation grade C)
Emergency treatment should start without delay and should be performed aggressively during febrile illness, surgery and immunization within the vulnerable period for acute encephalopathic crises (up to age 6 years).

Home and outpatient emergency treatment

If the body temperature is less than 38.5°C and the child is not vomiting and is tolerating the 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 period patients should be reassessed every 2 hours regarding state of consciousness, fever and food tolerance. If this treatment is successful and no worrying signs or symptoms occur, natural protein should be reintroduced stepwise during the next 24–48 hours. Table 2 summarizes recommended best practice based on the clinical experience of the GDG.

Table 2 Home/outpatient emergency treatment

	Maltodextran/dextrose		
Age (years)	(%)	(kcal/100 ml p.o.)	Volume (ml) per day p.o.
A. Maltodextran/dextrose[a]			
0–1	10	40	min. 150/kg
1–2	15	60	120/kg
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 per day p.o. (see also Table 1)		
C. Pharmacotherapy			
L-Carnitine	Double carnitine intake: 200 mg/kg per day p.o.		
Antipyretics[b]	If body temperature increases above 38.5°C (101°F), antipyretics such as ibuprofen (10–15 mg/kg per single dose, 3–4 doses daily) should be administered.		

AA, Lys-free, Trp-reduced amino acids supplements
[a]Solutions should be administered every 2 hours day and night. If neonates and infants already receive a specific dietary treatment, such as Lys-free, Trp-reduced AA supplementation, this can be continued but should be fortified by maltodextran. Patients should be re-assessed every 2 hours
[b]Paracetamol administration may be dangerous during acute metabolic decompensation (risk of glutathione depletion). Calculations for maltodextran/dextrose and protein intake should be based on the expected and *not* on the actual weight!

Inpatient emergency treatment

If the patient has recurrent vomiting, spiking temperature or even warning neurological signs, home/outpatient therapy is not safe and inpatient emergency treatment should be initiated immediately in a metabolic centre or the closest hospital (preferably under the guidance of a metabolic centre). Although there are no exact calorimetric data for GCDH deficiency, the experience from many metabolic centres is that energy should be increased to at least 120% of daily requirements to prevent the development of an acute crisis in GCDH deficiency (Kölker et al 2004; Monavari and Naughten 2000; Strauss et al 2003). Table 3 summarizes recommended best practice based on the clinical experience of the GDG.

Emergency treatment after age 6 years

Although no encephalopathic crisis has been documented after age 6 years (Bjugstad et al 2000; Kölker et al 2006; Strauss et al 2003), it cannot be excluded that febrile illness, surgery and immunization are completely harmless at this age group. Future observations are important to estimate the neurological vulnerability to these conditions more precisely.

Statement #18 (GCP)
Emergency treatment in children after age 6 years should be considered at least during severe illness. It should be performed similarly to that in the age group 0–6 years, with adaptation to the individual.

Management of neurological complications

Neurological disease is common, particularly in untreated patients, and the manifestations are varied. The most frequent neurological complications in GCDH deficiency are (1) movement disorders, (2) epilepsy, (3) subdural bleedings, and (4) bitemporal arachnoid cysts.

Management of movement disorders

The characteristic neurological sequel of these encephalopathic crises is a bilateral striatal injury (Suppl. Text 1) inducing a variable clinical picture. Dystonia is the predominant extrapyramidal symptom, often accompanied by spasticity (Hoffmann et al 1996; Kyllerman et al 1994).

Statement #19 (GCP)
In all patients with GCDH deficiency, expert neurological evaluation should be performed by a neuropaediatrician and/or later on by a neurologist to identify clearly the kind of movement disorder. In addition, dietitians, physiotherapists, occupational therapists, orthopaediatrists, seating and speech specialists, and providers of communication aids should be consulted to provide multi-professional support for children with movement disorders.

Table 3 Inpatient emergency treatment

	Increase to min. 120% of age-dependent daily requirements			
Calories	0–6 months	7–12 months	1–3 years	4–6 years
A. Energy requirement[a]				
120% of dietary recommendations (kcal/kg per day)	98–128	96–109	98–109	96–98
B. Intravenous infusions				
Glucose	15(−20) g/kg per day i.v.			
Lipids	Start with 1–2 g/kg per day i.v.; if possible increase stepwise to 2–3 g/kg per day i.v.			
Electrolytes	Electrolytes should be kept in the upper normal range (intermittent tubulopathy can occur during crises)			
Insulin	If persistent hyperglycaemia >150 mg/dl and/or glucosuria occurs, start with 0.05 IE insulin/kg per hour i.v. and adjust the infusion rate according to serum glucose (Warning! Increased intracellular uptake of potassium)			
L-Carnitine	100(–200) mg/kg per day i.v.			
C. Protein intake				
Natural protein	Stop for max. 24 (–48) hours, then reintroduce and increase stepwise up to 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 (Lys-free, Trp-reduced)	If tolerated, AA mixtures should be administered orally or by nasogastric tube according to maintenance therapy: 0.8–1.3 g/kg per day p.o. (see also: Table 1)			
D. Pharmacotherapy				
Antipyretics[b]	If temperature >38.5°C, e.g. ibuprofen 10–15 mg/kg per dose p.o.			
Antibiotics	Purposeful and timely administration			
Antiemetics	If vomiting; ondansetron 0.1 mg/kg per dose i.v. (max. 3 doses daily)			
Diuretics	If diuresis is less than 3–4 ml/kg per day: furosemide 0.5–1.0 mg/kg per dose i.v. (3–4 doses per day). (Warning! Rebound and electrolyte loss)			
Bicarbonate	If acidosis; alkalinization 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[c], carnitine state, blood culture, amylase/lipase[d], creatine kinase[d]			
Urine	Ketone bodies, pH			
Vital signs	Heart rate, blood pressure, temperature, diuresis; Glasgow Coma Scale if reduced consciousness			

[a]All calculations for energy requirement and intravenous infusions should be based on the expected and *not* on the actual weight!
[b]Paracetamol administration may be dangerous in acute metabolic decompensation (risk of glutathione depletion)
[c]During the recovery phase
[d]Useful for monitoring in severe illness to detect pancreatitis (amylase/lipase) or rhabdomyolysis (creatine kinase)

Drug therapy

Movement disorders in GCDH deficiency are difficult to treat and the efficacy of a drug cannot be predicted precisely.

Baclofen: Baclofen is generally used for symptomatic treatment of spasticity but is also common for the long-term treatment of dystonia. Together with diazepam it is the most widely used and efficacious drug in GCDH deficiency (Hoffmann et al 1996; Kyllerman et al 1994). Oral baclofen should be used in dosages according to general recommendations. Intrathecal baclofen administration has been used with success in a few children with severe dystonia (Kyllerman et al 2004).

Benzodiazepines: Diazepam and clonazepam have been successfully used in treating dystonia (Hoffmann et al 1996; Kyllerman et al 1994). 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.

Anticholinergic drugs: Trihexyphenidyl is effective in treating dystonia (Burlina et al 2004). High doses of the drug can be reached only if trihexyphenidyl is increased slowly. Adverse effects such as blurred vision and dry mouth are temporary. Memory deficit and confusion usually persist and require dosage reduction. Adverse effects are encountered more frequently in adults than in children.

Botulinum toxin: Botulinum toxin type A (BT-A) has recently been reported as an alternative therapy for focal dystonia in an affected girl (Burlina et al 2004). An additional nine patients (aged 7–21 years) have been successfully treated with BT-A (S. Kölker, personal communication, 2006). BT-A therapy is not or is only partially efficacious if started after the manifestation of significant joint contractures. BT-A should be administered by a neurophysiologist or neurologist with experience of this treatment. Some patients can develop immunity against the toxin, precluding further therapy; therefore, BT-A is usually administered every 3 months to minimize the formation of antibodies against the toxin.

Drugs for the movement disorder of no proven effect or with adverse effects: Some antiepileptic drugs (e.g. vigabatrin, carbamazepine, valproate) have been used for therapy of movement disorders in GCDH deficiency (Hoffmann et al 1996; Kyllerman et al 1994; Kyllerman et al 2004). *Vigabatrin* and *valproate* had little to no effect. *Carbamazepine* was always unequivocally ineffective. *Valproate* effectively competes with GA for esterification with L-carnitine. It may promote disturbances in the mitochondrial acetyl-CoA/CoA ratio and thus should not even be tried in GCDH deficiency. There is no improvement of the extrapyramidal syndrome with L-*dopa* (Kyllerman et al 2004) or *amantadine* (G. F. Hoffmann, personal communication, 2006).

Statement #20 (Recommendation grade D)
The benefit of affected patients from pharmacotherapy is uncertain. Pharmacotherapy of movement disorders should follow some general rules:

- 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.
- Trihexyphenidyl should be considered as second-line treatment for dystonia, in particular in adolescents and adults.
- Botulinum toxin A should be considered as additional therapy for severe focal dystonia.
- Antiepileptics, L-dopa and amantadine should not be used for the therapy of movement disorders in GCDH deficiency.

Neurosurgery

Stereotactic surgery (pallidotomy) for severe generalized dystonia has been reported for three patients. The results reported in two patients were unsatisfactory (Strauss et al 2003), whereas short-term improvement was described in the other (Rakocevic et al 2004).

Statement #21 (Recommendation grade 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 therapy

The frequency of seizures is increased in GCDH deficiency during or following acute encephalopathic crises, although there is considerable variability in different cohorts (Greenberg et al 2002; Hoffmann et al 1996; Kölker et al 2006; Kyllerman et al 2004; Strauss et al 2003). Dystonic movements may be mistaken as seizures. No study has investigated the comparative efficacy of antiepileptic drugs in GCDH deficiency. However, phenobarbital, phenytoin, carbamazepine, topiramate and lamotrigine have all been used.

Statement #22 (GCP)
Diagnosis, choice of antiepileptic drug therapy and management of seizures in GCDH deficiency should follow existing guidelines (e.g. SIGN guideline #81: Diagnosis and management of epilepsies in children and young people). Since the confirmation and classification of epilepsies has important practical implications, the diagnosis of epilepsy and choice of antiepileptic drugs should be made by a paediatric neurologist or paediatrician with expertise in childhood epilepsy.

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

Subdural haemorrhage and arachnoid cysts

Diagnosis

Subdural haemorrhage may occur at any age but peaks during the age of maximal extent of macrocephaly, i.e. infancy (Hartley et al 2000; Köhler and Hoffmann 1998; Woelfle et al 1996). 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 asymptomatic. Subdural haemorrhage in GCDH deficiency may be mistaken with shaken baby syndrome and vice versa (Hartley et al

2001; Morris et al 1999). Bitemporal arachnoid cysts have been described in some affected patients and result in a high suspicion for GCDH deficiency (Hald et al 1991; Jamjoom et al 1995; Martinez-Lage et al 1994; Lüchterath et al 2000), whereas unilateral arachnoid cysts are a rare occurrence in this disease.

Statement #23 (Recommendation grade D)
Children with subdural bleeding and/or bitemporal arachnoid cysts should be investigated for GCDH deficiency, in particular if occurring in combination with macrocephaly and/or movement disorders.

Statement #24 (Recommendation grade D)
GCDH deficiency should be excluded in children with suspected shaken baby syndrome.

Neurosurgery

Neurosurgical interventions have been performed in a small number of affected patients with arachnoid cysts and subdural haemorrhage (Hald et al 1991; Lütcherath et al 2000; Martinez-Lage et al 1994; Woelfle et al 1996). The majority of these patients had a poor neurological outcome or had no significant neurological improvement. In particular, in undiagnosed patients who do not receive specific metabolic treatment, neurosurgical interventions can precipitate an encephalopathic crisis. Subdural haemorrhage may regress without neurosurgical intervention if metabolic treatment is intensified (E. Naughten, personal communication, 2005).

Statement #25
Neurosurgical interventions in arachnoid cysts and subdural haemorrhage 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 shift (Recommendation grade D).
The metabolic management during and after surgical interventions should be supervised by a metabolic specialist to decrease the risk of acute encephalopathic crises (GCP).

Monitoring therapy

Major complications of GCDH deficiency

GCDH deficiency may be complicated by (1) acute encephalopathic crises, (2) subdural haemorrhage, or (3) malnutrition. Whereas encephalopathic crises manifest acutely, subdural bleedings and malnutrition develop insidiously.

Investigative procedures

General aims

The aim of regular monitoring of therapy is to assess the efficacy of treatment and any possible complications or side-effects. In children, monitoring should include an evaluation of psychomotor development and growth. Therapy monitoring shall include those tests that influence therapeutic decisions and should be *preventive* in its overall approach.

Statement #26 (GCP)
At present, there is no reliable marker that predicts the outcome of GCDH deficiency.

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 a wide variety of investigations, ranging from general paediatric parameters (anthropometrics, milestones of psychomotor development), through neurological assessment (quality, extension, and intensity of movement disorders) to specific psychological tests. Expertise from general paediatricians, metabolic specialists, and dietitians from metabolic centres should be included in the evaluation of patients in an integrative way. In addition, consultations from other specialists (e.g. child neurologists, psychologists, physiotherapists, ophthalmologists) should be considered as necessary.

Statement #27 (GCP)
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 intensified at any age when there are new complications (disease- or therapy-related) or non-compliance.

Routine biochemical monitoring

Laboratory monitoring is essential to detect insufficient supply of nutrients *before* clinical manifestation of malnutrition. At present, there is no reliable biochemical marker that is useful for the monitoring of maintenance treatment (Mühlhausen et al 2004).

Organic acids: Decreases in the urinary concentrations of GA and 3-OH-GA have been demonstrated in high excretors following dietary treatment (Hoffmann et al 1991; Hoffmann

et al 1996; Strauss et al 2003), whereas this biochemical response is usually not found in the urine of low excretors (Greenberg et al 2002). At present, there is no evidence that urinary concentrations of GA and 3-OH-GA correlate with the long-term clinical outcome (Christensen et al 2004; Kölker et al 2006). However, CNS concentrations of GA and 3-OH-GA are strikingly high in both high and low excretors (Funk et al 2005; Goodman et al 1977; Külkens et al 2005; Leibel et al 1980). Dramatic decreases in CNS concentrations of GA and 3-OH-GA have been demonstrated in patients being effectively treated with a Lys-restricted diet prior to death (Bennett et al 1986; Kölker et al 2003). Therefore, monitoring of urinary GA and 3-OH-GA concentrations may not give reliable information about the CNS concentrations. The currently available magnetic resonance spectroscopy systems lack sensitivity to be useful for the follow-up of cerebral GA and 3-OH-GA concentrations.

Statement #28 (GCP)
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, but should not be considered for regular long-term follow-up investigations.

Amino acids: Analysis of amino acids in plasma is useful to ensure that the nutrition is not being compromised, in particular during dietary treatment and in children with feeding problems (Müller and Kölker 2004; Yannicelli et al 1994). Trp should be assayed by specific HPLC analysis (or MS/MS analysis) as conventional AA analysis is not satisfactory.

Statement #29
Amino acids in plasma (fasting or at least 4 hours postprandially) should be monitored during dietary treatment (Recommendation grade D).

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 (GCP).

Carnitine status: Carnitine supplementation prevents secondary depletion of free carnitine and improves the outcome (Bjugstad et al 2000; Hoffmann et al 1996; Kölker et al 2006; Seccombe et al 1986). Carnitine status in plasma assessed by HPLC or MS/MS analysis allows correct quantification and gives valuable information on compliance. MS/MS analysis in dried blood spots is also useful to detect secondary carnitine depletion but is less accurate than measurement of plasma levels.

Statement #30 (Recommendation grade D)
Carnitine status in plasma should be monitored to detect secondary carnitine depletion.

Acylcarnitine profile: This is a valuable tool for neonatal and high-risk screening but not for biochemical monitoring. C5DC will increase markedly with the start of carnitine supplementation.

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 (Yannicelli et al 1994).

Table 4 summarizes recommended best practice based on the clinical experience of the GDG on routine laboratory monitoring in GCDH deficiency.

Biochemical monitoring during acute illness

Vomiting, diarrhoea and reduced intake of nutrients and fluids increases the risk of dehydration, electrolyte loss, acidosis, and subsequently acute encephalopathic crises (Hoffmann et al 1996; Kölker et al 2006; Kyllerman et al 2004; Strauss et al 2003). Imbalances in the metabolic state, hydration and serum electrolytes, and complications should be identified on admission and emergency treatment adjusted accordingly. Table 5 summarizes recommended best practice based on the clinical experience of the GDG on laboratory monitoring during acute illness in GCDH deficiency.

Neuroradiological monitoring

Cranial MRI and CT scans in affected patients often demonstrate a characteristic pattern of grey and white matter changes and abnormalities of CSF spaces that should prompt a high suspicion for the diagnosis of GCDH deficiency (Suppl. Table 7). MRI scans, in particular those using echo-planar imaging spin-echo (EPI-SE) or apparent diffusion coefficient (ADC) maps, detect striatal lesions earlier and more reliably than CCT scans (Brismar and Ozand 1995; Desai et al 2003; Elster 2004; Neumaier-Probst et al 2004; Oguz et al 2005; Twomey et al 2003). Some of these neuroradiological changes can also be detected by ultrasound (Forstner et al 1999), as early as during the last trimester of pregnancy (Lin et al 2002).

Indication: Neuroradiological findings are undoubtedly valuable for indicating possible GCDH deficiency in undiagnosed patients; however, the benefit from serial MRI or CCT investigations is unclear for several reasons: (1) Chronic neuroradiological abnormalities do not yet influence the clinical decision-making on metabolic treatment. (2) The risk-to-benefit ratio for neurosurgical interventions is poor. (3)

Table 4 Routine biochemical monitoring in GCDH deficiency

Parameter	Rationale	Frequency at age		
		0–12 months	1–6 years	>6 years
Amino acids (plasma)	General nutritional status	Every 1–2 months	Every 3 months	Every 6 months
Trp (plasma; HPLC)	Trp depletion	If Lys- *and* Trp-free AA mixtures are used; in all children with feeding problems		
Carnitine (plasma or serum)	Avoid secondary depletion, check for compliance	Every 1–2 months	Every 3 months	Every 6 months
Complete blood cell count	Routine surveillance, depletion of iron, folate, or cobalamin	Every 6 months	Every 6 months	Every 6 months
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 months	Every 6 months	Every 12 months
Transaminases	Routine surveillance, metabolic decompensation	Every 3 months	Every 6 months	Every 12 months

Table 5 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

Sedatives that are often required for obtaining MRI and CCT scans in infants may have adverse effects.

Statement #31 (GCP)
Neuroradiological investigations should be performed in case of neurological deterioration. To reduce sedatives in newborns and infants, neuroradiological investigations should be performed within physiological sleeping times, most preferably after feeding.

Methods: After clinical stabilization or improvement of patients who have developed neurological disease, the 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 content of the developing infant brain. Water content is considerably higher in the brain in neonates than in infants and decreases with age, necessitating increased repetition time (TR) and echo time (TE) to compensate for the longer relaxation times. 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, EPI-SE MR imaging including ADC maps should also be obtained, since it detects acute neurological damage more precisely and earlier than conventional MRI techniques. A proposal for a standardized MRI protocol is given in Suppl. Table 14. 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.

A short version of the guideline is provided at Suppl. Table 15.

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