

Evidence table of systematic literature search*

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

Level 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.

Authors	Title	Study design	Results / Conclusions
<p>Heringer et al (2010) Ann Neurol 68: 743-752.</p> <p>→ see also: Kölker et al (2007)</p>	Use of guidelines improves the neurological outcome in glutaric aciduria type I.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Prospective multi-centre follow-up study in Germany (1999-2009) - n=52 patients identified by newborn screening, n=3 patients with a low excretor phenotype missed by newborn screening - Treatment protocol: According to the guideline proposal (Kölker et al. J Inherit Metab Dis 2007; 30: 5-22) - Outcome was assessed by the occurrence of acute encephalopathic crises, the severity of motor disorder (Barry Albright Dystonia Scale and other predefined score), and survival. - Effect of treatment according to guideline, follow-up by a metabolic centre, migrational background and biochemical phenotype on the neurological outcome was evaluated. 	<ul style="list-style-type: none"> - Patients treated in full accordance with treatment recommendations and followed by metabolic centres had the best outcome (5% of patients had movement disorder). Overall, 11% of patients of neonatally diagnosed patients had an acute encephalopathic crisis and, subsequently, develop severe movement disorder; further 11% of patients develop insidious motor delay without preceding crisis and showed a mild to moderate movement disorder. - 13 patients with the low excretor phenotype were identified correctly by newborn screening, whereas three low excreting patients were known to be missed, and two of them presented with acute encephalopathic crisis and severe movement disorder. - Deviations from basic metabolic treatment resulted in an intermediate outcome (44% of movement disorder), whereas disregard of emergency treatment was associated with a poor outcome (100% movement disorder) - Treatment regimens deviating from recommendations significantly increased the risk for movement disorder (Odds ratio=35). Accordance to emergency treatment (Odds ratio=185) had a higher impact on the outcome the accordance to basic treatment (Odds ratio=14). - Barry-Albright Dystonia Scale does not adequately assess the severity of the complex movement disorder in infants and young children if they present not only with dystonia but also with severe axial hypotonia. - Conclusion: This is the first study investigating the beneficial effect of previous treatment recommendations showing that both basic and emergency treatment is required to receive an optimal outcome and that children followed by metabolic centres had the best outcome.
Nasser et al (2009) Cochrane Database Syst Rev 2: CD006659.	Carnitine supplementation for inborn errors of metabolism.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Systematic review of randomised controlled trials and quasi-randomized controlled trials comparing carnitine supplementation (in different dose, frequency, and duration) versus placebo in children and adults diagnosed with an inborn error of metabolism, including GA-I 	<ul style="list-style-type: none"> - No RCT trials were found. - Conclusions: There are no published or ongoing randomised controlled clinical trials relevant to this review question. Therefore, in the absence of any high level evidence, clinicians should base their decisions on clinical experience and in conjugation with preferences of the individual where appropriate. This does not mean that carnitine is ineffective or should not be used in any inborn error of metabolism. Methodologically sound trials are required. It should be

* Die Evidenztabelle wurde von der international zusammengesetzten Leitliniengruppe in englischer Sprache erstellt.

			considered whether placebo-controlled trials in potentially lethal diseases, e.g. GA-I, are ethical.
Watson et al (2006) Pediatrics 117 : S315-S319.	Newborn screening: toward a uniform screening panel and system – executive summary.	<u>Study design:</u> - ACMG convened a group, the Newborn Screening Expert Group - The expert group used a 2-tiered approach: first, specific evaluation of evaluation criteria by recognized experts; second, quantification data were subjected to an analysis of the evidence base for each specific screening criterion score. - Systematic review on 19 evaluation criteria on three categories: 1) clinical characteristics (e.g incidence, disease burden if not treated), 2) analytical characteristics of the screening test (e.g. availability and features of the platform); and 3) diagnosis, treatment, and management of the condition in acute and chronic forms (this criterion includes the availability of experienced health professionals). - Based on the categorical evaluation a sum score was generated allowing to identify the strengths and limitations for each condition tested and to summarize the results in a ranking list.	- Nearly 300 individuals from the United States and other countries completed the data collection instrument. - Many respondents provided information on multiple conditions, yielding information on nearly 4000 individual disease-specific responses. - MCAD deficiency, congenital hyperthyroidism, and PKU received the highest scoring, GA-I was scored within the upper third of conditions for which efficacious treatment and sufficient natural history information were considered to be appropriate for newborn screening. - The expert group identified 29 conditions (among them, GA-I) for which screening should be mandated. - Conclusion: Based on this GA-I is recommended for inclusion in the newborn screening disease panel.

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
Harting et al (2009) Brain 132: 1764-1782.	Dynamic changes of striatal and extrastriatal abnormalities in glutaric aciduria type I	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Retrospective study on 68 MRI studies of 38 patients (age range 9 days to 66 years) using a systematic and quantitative assessment of region-specific MRI abnormalities. - 18 patients had neurological symptoms and 21 patients had no neurological symptoms at time point of MRI study - First multiple rater MRI study for GA-I - Evaluation of neurological symptoms and developmental stage at time point of MRI using predefined scores to assess motor disability and standardized psychological tests (BSID, Wechsler, SON-R) 	<ul style="list-style-type: none"> - Major changes after acute encephalopathic crises were found in putamen, nucleus caudatus, globus pallidus and ventricles. Motor disabilities was associated with pathologic changes in these regions. - Analysis of empirical cumulative distribution frequencies, however, demonstrated that isolated pallidal abnormalities did not significantly differ over time in patients with and without crises. - A high frequency of extrastriatal abnormalities including immature gyral pattern, myelination delay and abnormal T2 signals in periventricular white matter, substantia nigra, thalamus, tractus tegmentalis centralis and dentate gyri was found in patients with and without crises. The clinical relevance of these findings remains to be elucidated. - Conclusions: The authors hypothesize that neuroradiological and neurological abnormalities in GA-I can be explained by overlaying episodes of cerebral alterations including maturational delay in utero, acute striatal injury during infancy and chronic progressive changes that may continue lifelong.
Kölker et al (2007) Pediatr Res 62: 357-363.	Decline of acute encephalopathic crises in children with glutaryl-CoA dehydrogenase deficiency identified by newborn screening in Germany.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Prospective multi-centre follow-up study in Germany - 38 patients identified by newborn screening and 62 patients from a historical cohort diagnosed after the onset of neurological symptoms. - Median age at latest report: a) NBS group: 49 months; b) historical cohort: 133 months. - Standardized treatment protocol for the NBS group. - Outcome parameters: Survival, motor disability (using predefined scores), gross motor milestones, anthropometrical parameters (height, weight, body mass index, head circumference) 	<ul style="list-style-type: none"> - Newborn screening in combination with standardized metabolic treatment using low lysine diet, carnitine supplementation and intermittent emergency treatment during intercurrent illness significantly improves the outcome (11% of patient had encephalopathic crises in the NBS group and 77% of patients in the historical cohort). - Numbers needed to treat to prevent one encephalopathic crises = 1.50 patients - First encephalopathic crisis in the NBS group occurred by a median age of 10 months (range: 1-37 months). - The study does not allow evaluation of the individual impacts of dietary treatment, carnitine supplementation, or emergency treatment on outcome. - The study shows that low lysine diet does not impair growth. - There is no evidence that newborn screening selects patients with a mild disease variants. - No patient was known to be missed during the study period, however, there is no regular tracking system in Germany. - Seven patients with a low-excreting phenotype were identified by newborn screening. - Conclusions: Newborn screening in combination with intensive metabolic management improves the short-term outcome of GA-I patients.
Kölker et al (2006) Pediatr Res; 59: 840-847.	Natural history, outcome, and treatment efficacy in children and adults with glutaryl-CoA dehydrogenase deficiency.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Questionnaire-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. 	<p>Mode of diagnosis</p> <ul style="list-style-type: none"> - n=61 asymptomatic patients (neonatal screening, high-risk screening, siblings, macrocephaly); n=218 symptomatic patients (acute encephalopathic crisis, insidious-onset) <p>Acute encephalopathic crisis</p> <ul style="list-style-type: none"> - The majority of crises occurred before age 3 years; no crisis was reported after age 6 years; - Most patients (70%) had only one crisis and

			<p>revealed a moderate to severe movement disorder.</p> <p>Mortality</p> <ul style="list-style-type: none"> - Approximately 20% of all patients died. - The cause of death often remained unknown, pneumonia was the most frequently considered cause of death; - Deceased patients showed the highest morbidity score and the highest number of acute crises. <p>Variables that influence the outcome</p> <p>Positive effect:</p> <ul style="list-style-type: none"> - Early diagnosis (< 3 months of age), i.e. before the window for acute striatal damage opens - Oral carnitine supplementation - Lysine-restricted diet <p>No effect:</p> <ul style="list-style-type: none"> - Riboflavin - Protein-restricted diet <p>Not evaluated:</p> <ul style="list-style-type: none"> - Emergency treatment could not be evaluated by this approach, since important parameters (hours of delay, exact protocols used) remained unknown in included patients. <p>Genotype phenotype correlation</p> <ul style="list-style-type: none"> - No correlation between residual GCDH deficiency and neurological outcome. <p>Open questions</p> <ul style="list-style-type: none"> - Nature of insidious-onset type (distinct disease course or abortive crisis); - Individual risk and protection factors to suffer an acute crisis.
<p>Strauss et al (2003) Am J Med Genet 121C:38-52.</p> <p>→ <u>see also</u>: Morton et al (1991)</p>	<p>Type I glutaric aciduria, part 1: Natural history of 77 patients</p>	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Monocentric study - 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 <p>Maintenance treatment:</p> <ul style="list-style-type: none"> - Natural protein (1-1.25 g/kg/d), - Calories 100-115 kcal/kg/d; - Carnitine 100 mg/kg/d - Riboflavin 10 mg/kg/d - <u>Additional treatment:</u> 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) <p>Emergency treatment:</p> <ul style="list-style-type: none"> - 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. 	<p>Basal ganglia injury:</p> <p>a) <u>Symptomatic</u>: 85 % (non-Amish) – 94 % (Amish)</p> <p>b) <u>Pre-symptomatic</u>: 35 % (Amish)</p> <p>Degree of motor disability:</p> <p>a) <u>Symptomatic (Amish and non-Amish)</u>: 12 % asymptomatic, 14% subtle and mild, 74 % moderate and severe,</p> <p>b) <u>Pre-symptomatic (Amish)</u>: 65 % asymptomatic, 9% subtle and mild, 26 % moderate and severe.</p> <p>Acute encephalopathic crises :</p> <p>Occurred until age 18 months</p>
Strauss et al	Multimodal imaging of	<u>Study design:</u>	- Delineated three stages of striatal injury: 1)

<p>(2007) Brain 130: 1905-1920.</p> <p>→ <u>see also</u>: Strauss et al (2003)</p>	<p>striatal degeneration in Amish patients with glutaryl-CoA dehydrogenase deficiency.</p>	<p>- Retrospective, monocentric MRI study including T1, T2 and ADC maps</p> <p>- 25 Amish patients homozygous for c.1296C>T (p. A421V).</p>	<p>acute stage, within 24 h of motor regression, characterized by cytotoxic edema within the basal ganglia, cerebral oligemia, and rapid transit of blood throughout gray matter; 2) subacute stage, 4-5 days after the onset of clinical signs, characterized by reduced striatal perfusion and glucose uptake, and supervening vasogenic edema; and 3) a chronic stage of striatal atrophy.</p> <p>- ADC maps revealed that at least two of the six patients with insidious motor delay suffered striatal injuries before or shortly after birth, followed by latent periods of several months before disability was apparent.</p> <p>- Therapy: Intravenous fluid and dextrose therapy for illnesses during the first 2 years of life was thought to be the only intervention that was clearly neuroprotective in this cohort. The authors, however, only show that newborn screening was neuroprotective. Metabolic maintenance treatment (dietary treatment and carnitine supplementation) had no significant effect (however, the groups tested were quite small).</p> <p>- Conclusions: Acute and insidious presentations may occur by similar mechanisms, and differ only with regard to the timing of injury</p>
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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
Bijarnia et al (2008) J Inherit Metab Dis 31 : 503-507.	Glutaric aciduria type I: outcome following detection by newborn screening.	<u>Study design:</u> - Retrospective study in New South Wales (Australia) - Follow-up of 10 patients identified during the last decade either clinically (n=3) or by newborn screening (n=7) - Standardized treatment: low lysine diet (supplemented with precursor-free amino acid mixtures), carnitine supplementation and intermittent emergency treatment during intercurrent illness	- Prevalence was 1 in 90,000 newborns - Clinically diagnosed patients were all symptomatic: severity scores 3, 5 and 9 (out of 9) - Six of 7 patients diagnosed neonatally remained asymptomatic, one patient had a severe decompensation at age 7 months (despite full management advice and treatment), and later died. - Conclusion: the study confirms that newborn screening in combination with intensive metabolic management significantly reduces the frequency of severe neurological complications in GA-I.
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.	<u>Study design:</u> - 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.
Boneh et al (2008) Mol Genet Metab 94 : 287-291. → see also: Beauchamp et al (2009)	Newborn screening for glutaric aciduria type I in Victoria: treatment and outcome.	<u>Study design:</u> - Prospective follow-up study of GA-I patients identified by newborn screening in Victoria, Australia, between October 2001 and September 2007 - Assessment of neurological outcome using standardized neuropsychological tests. - Standardized treatment protocol: protein 2.0-2.5 g/kg per day (no precursor-free amino acid supplements), 100 mg/kg per day carnitine and emergency treatment during intercurrent illness.	- Prevalence: 1 in 65,275 - Neuropsychological examinations revealed normal to high cognitive and gross motor function in all patients; the manifestation of encephalopathic crises and dystonia was prevented in all of them (35 hospital admissions for emergency treatment). - Some deficiencies in fine motor activities and speech abnormalities were identified. This has been published in detail in another article of the same authors → Beauchamp et al. (2009). - Conclusions: The study confirms that newborn screening in combination with intensive metabolic management improves the outcome in GA-I. The authors highlight that more in-depth consideration of speech and language function is necessary to document specific deficits in these children and plan proactive interventions.
Busquets et al (2000) Pediatr Res 48 : 315-322.	Glutaryl-CoA dehydrogenase deficiency in Spain: evidence of two groups of patients, genetically and biochemically distinct.	<u>Study design:</u> - Cohort study of 43 Spanish patients (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	Biochemical and clinical presentation - n=26 high excretors (A293T, R402W), 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.
Gitiaux et al (2008) Mov Disord 23 : 2392-2397.	Spectrum of movement disorders associated with glutaric aciduria type 1 : a study of 16 patients.	<u>Study design:</u> - Prospective study in France - n=16 patients diagnosed symptomatically - Prospective follow-up and standardized neurological evaluation - Retrospective analysis of medical records	- A complex movement disorder was found which was best described as generalized dystonia superimposed on baseline axial hypotonia. - With aging, the movement disorder tended to evolve from mobile to fixed dystonia and to

		<p>and MRI studies of the same patients</p> <ul style="list-style-type: none"> - Movement disorder was video taped and two raters have evaluated it independently - MRI scans were blinded and were reviewed by neuroradiologist, and severity scored as described previously (→ Twomey et al 2003) - No validated dystonia rating scales (e.g. Burke Fahn Marsden Scale or Barry Albright Dystonia Scale) were used to assess the severity of motor dysfunction. 	<p>be associated with akinetic-rigid parkinsonism. Prominent orofacial involvement was a consistent feature in GA-I patients with movement disorders, resulting in speech disorders with features of combined hyperkinetic dysarthria and speech apraxia.</p> <ul style="list-style-type: none"> - Videos of two patients are included in the online version of the article. - Conclusion: These gradual changes in the motor type should taken into consideration for rehabilitation and for patients' selection and evaluation in therapeutic trials. The time course of the movement disorder may reflect the response of the developing brain to static damage that occurred early in life, rather than being an ongoing disease process. This natural disease course of movement disorder during aging and disease progression is quite similar to that observed in other neurometabolic diseases with hyperkinetic disorders, such as Lesch-Nyhan disease and GM1 gangliosidosis.
<p>Hennermann et al (2009) J Inherit Metab Dis, DOI: 10.1007/s10545-009-9017-6.</p>	<p>False-positive newborn screening mimicking glutaric aciduria type I in infants with renal insufficiency.</p>	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Retrospective monocentric study - Newborn screening results on 173,846 newborns from January 2005 to December 2008. - Evaluation of C5DC elevation in 11 patients in whom C5DC has remained elevated after recall. - First systematic study evaluating the impact of renal insufficiency on elevated C5DC in newborn screening. 	<ul style="list-style-type: none"> - None of the 11 newborns with elevated C5DC had GA-I. Five of them had congenital and six of them acquired renal insufficiency. - C5DC was shown to be significantly associated with renal dysfunction and was significantly higher in infants with congenital renal insufficiency than in those with acquired renal insufficiency. - Creatinine correlated with C5DC and with various C5DC/acylcarnitine ratio. - Conclusion: Renal insufficiency is an important pitfall of C5DC screening.
<p>Hoffmann et al (1996) Neuropediatrics 27: 115-123.</p> <p>→ <u>see also:</u> Hoffmann et al (1991)</p>	<p>Clinical course, early diagnosis, treatment, and prevention of disease in glutaryl-CoA dehydrogenase deficiency.</p>	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - 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); <p><u>Treatment:</u></p> <p>a) Maintenance treatment:</p> <ul style="list-style-type: none"> - 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) <p>b) Emergency treatment:</p> <ul style="list-style-type: none"> - Glucose and electrolyte infusion (no exact protocol published), - Fever control/antipyretics - Carnitine dosage not specified. 	<p>Clinical presentation</p> <p>a) Pre-symptomatic children:</p> <ul style="list-style-type: none"> - 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". <p>b) Symptomatic children:</p> <ul style="list-style-type: none"> - No clear benefit (but further neurologic deterioration may have been prevented) - 1/78 asymptomatic, 13/78 moderate handicap, 64/78 severe handicap, 16/78 died; - Neurological deterioration: Insidious-onset type 19%, encephalopathic crisis 81%. <p>Monitoring:</p> <ul style="list-style-type: none"> - Risk of tryptophan depletion using lysine- and tryptophan-reduced diet if not monitored.
<p>Kyllerman et al (2004) Eur J Paediatr Neurol. 8 :121-129.</p> <p>→ <u>see also:</u> Kyllerman et (1994)</p>	<p>Long-term follow-up, neurological outcome and survival rate in 28 Nordic patients with glutaric aciduria type 1.</p>	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - 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. 	<p>Morbidity</p> <ul style="list-style-type: none"> - Six patients died (21%) - At 10 years of age the cumulative survival rate was 89% and at 35 years 44%. <p>Movement disorders</p> <ul style="list-style-type: none"> - Dystonia (n=20), dyskinesia (n=4), slight spastic signs (n=3) <p>Acute encephalopathic crises</p> <ul style="list-style-type: none"> - The onset was acute encephalopathic in 24 patients and insidious in 3. <p>Treatment</p> <ul style="list-style-type: none"> - 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.
<p>Monavari and Naughten (2000) Arch Dis Child 82:</p>	<p>Prevention of cerebral palsy in glutaric aciduria type I by</p>	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Prospective follow-up study in Ireland, - n=6 asymptomatic patients, 	<p>Outcome</p> <p>a) Asymptomatic patients: 1/6 crises, 4/6 no neurologic abnormality, 1/6 fluctuating</p>

<p>67-70.</p> <p>→ see also: Naughten et al (2004); Twomey et al (2003)</p>	<p>dietary management</p>	<p>- n=6 symptomatic patients; <u>Treatment:</u> → See Naughten et al (2004)</p>	<p>neurologic problems, 1/10 died (pneumonia, no adequate emergency treatment, prematurity, placenta previa); b) Symptomatic patients: 6/6 movement disorders, 5/6 died</p>
<p>Naughten et al (2004) J Inherit Metab Dis 27: 917-920.</p> <p>→ see also: Monavari and Naughten (2000); Twomey et al (2003)</p>	<p>Glutaric Aciduria Type I, Outcome in the Republic of Ireland</p>	<p><u>Study design:</u> - Prospective follow-up study in Ireland (1988-2004; 16 years), - n=10 asymptomatic patients, - n=11 symptomatic patients; <u>Treatment:</u> Maintenance 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.</p>	<p>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.</p>

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

Authors	Title	Study design	Results / Conclusions
Beauchamp et al (2009) J Inherit Metab Dis, DOI: 10.1007/s10545-009-1167-z. → <u>see also</u> : Boneh et al (2008)	Cognitive, behavioural and adaptive profiles of children with glutaric aciduria type I detected by newborn screening.	<u>Study design:</u> - Case series (n=4) of children with GA-I diagnosed by newborn screening (n=3) or through cascade screening (n=1) - A comprehensive battery of standardized tests was administered including measures of intellectual function, attention/memory, as well as behavioural and adaptive skills. - For further details are published in Boneh et al. 2008	- The results reveal overall average cognitive outcomes. - Subtle, but significant fine motor and articulation deficits were observed. - Conclusion: These findings highlight the importance of in-depth assessments of all aspects of neuropsychological function in patients with GA-I and provide a basis for future neuropsychological assessment in similar groups of children. This allows for planning of early and adequate therapeutic interventions.
Bennett et al (1986) Eur J Pediatr 145: 403-405. → <u>see also</u> : Bjugstad et al (2000)	Glutaric aciduria type 1: Biochemical investigations and post mortem findings.	<u>Study design:</u> - 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.	<u>Study design:</u> - 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. → <u>see also</u> : Bjugstad et al (2000)	Treatment of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria).	<u>Study design:</u> - Intervention study (each 1 week: lysine/tryptophan-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 lysine/tryptophan-reduced, low-protein diet, and riboflavin; - “difficulties to accept lysine/tryptophan-reduced diet” - Clinical improvement during low-protein and lysine/tryptophan-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: 675-683.	CT and MR of the brain in glutaric aciemia type I: a review of 59 published cases and a report of 5 new patients.	<u>Study design:</u> - Clinical and neuroradiological investigations in glutaric aciduria type I - Report on n=5 prospectively followed patients - Review on n=59 patients	Clinical findings - In half the patients macrocephaly was present, and in half the onset was acute, often following infection and mimicking 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 glutaric aciduria type I, and if combined with basal ganglia lesions is almost pathognomonic, especially in a child with macrocephaly.

<p>Burlina et al (2004) J Inherit Metab Dis 27 : 911-915.</p>	<p>Management of movement disorders in glutaryl-CoA dehydrogenase deficiency : Anticholinergic drugs and botulinum toxin as additional therapeutic options.</p>	<p><u>Study design:</u> Follow-up study on 4 Italian patients - Evaluation of movement disorders after symptomatic treatment with different drugs</p>	<p>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.</p>
<p>Cerisola et al (2009) Pediatr Neurol 40 : 426-431.</p>	<p>Seizures versus dystonia in encephalopathic crisis of glutaric aciduria type I.</p>	<p><u>Study design:</u> - Retrospective monocentric study based on clinical history of GA-I patients with encephalopathy seen at the Sant Joan de Déu Hospital in Barcelona - n=13 patients confirmed biochemically and genetically - Evaluation of biochemical and clinical parameters as well as EEG.</p>	<p>- 12/13 patients had paroxysmal episodes at onset. Other clinical features included irritability (12/13), neurologic depression (11/13) and hypotonia (7/13). All patients evolved to dystonic tetraparesis. - Thirty-five EEGs were recorded in the acute stage and during the first year of follow-up. Spike discharges were only seen in 2 of the 13 patients, and 8 had slow background activity. No patient developed seizures during follow-up. - Conclusions: Most paroxysmal movements seen in symptomatic GA-I patients appear to be dystonic episodes but not epileptic seizures.</p>
<p>Chow et al (1988) Acta Neuropathol 76 : 590-594. → see also: Bjugstad et al (2000)</p>	<p>Neuropathology in glutaric acidemia type I.</p>	<p><u>Study design:</u> - Case reports and post mortem examinations in three children (2.5- 9 years of age) with fatal disease course.</p>	<p>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.</p>
<p>Desai et al (2003) Invest Radiol 38 : 489-496.</p>	<p>Magnetic resonance imaging of the brain in glutaric aciduria type I.</p>	<p><u>Study design:</u> - MRI study in n=4 children - Review of the literature</p>	<p>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.</p>
<p>Elster (2004) J Comput Assist Tomogr 28: 98-100.</p>	<p>Value of diffusion-weighted resonance imaging for diagnosing acute striatal necrosis.</p>	<p><u>Study design:</u> - Comparative study on CCT and MRI (T1, T2, DWI, MRS) - n=1 child</p>	<p>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 glutaric aciduria type I.</p>
<p>Fernandez-Alvarez et al (2003) Mov Disord 18: 1076-1079.</p>	<p>Hand tremor and orofacial dyskinesia : clinical manifestation of glutaric aciduria type I in a young girl.</p>	<p><u>Study design:</u> - Case report (n=1)</p>	<p>- 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)</p>
<p>Forstner et al (1999) Pediatr Radiol 29 : 138-</p>	<p>Glutaric aciduria type I: ultrasonographic demonstration of</p>	<p><u>Study design:</u> - Comparative study on US, CCT and MRI - n=6 children</p>	<p>Neuroradiological findings - Macrocephaly was found in all patients, being present in three children at birth or</p>

143.	early signs.		<p>developing rapidly within the first weeks of life.</p> <ul style="list-style-type: none"> - 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. <p>Conclusions</p> <ul style="list-style-type: none"> - 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.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - 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}). 	<p>Clinical presentation and therapy</p> <ul style="list-style-type: none"> - 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. <p>Post mortem examination</p> <ul style="list-style-type: none"> - 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. → <u>see also:</u> Bjugstad et al (2000)	Glutaric aciduria: a 'new' inborn error of amino acid metabolism.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Presentation of the two index cases (brother and sister) with this disease. 	<p>Clinical presentation</p> <ul style="list-style-type: none"> - Description of a novel neurodegenerative disease starting at about 6 months of age and characterized by opisthotonus, dystonia, and athetoid posturing. <p>Biochemical presentation</p> <ul style="list-style-type: none"> - 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. → <u>see also:</u> Bjugstad et al (2000)	Glutaric aciduria: Biochemical and morphologic considerations.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Case report and first published post mortem examination in one child (age 10 years) with fatal disease course. 	<p>Clinical presentation and therapy</p> <ul style="list-style-type: none"> - 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 hospitalizations 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. <p>Post mortem examination</p> <ul style="list-style-type: none"> - 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. → <u>see also:</u> Haworth et al (1991); Funk et al (2005)	Outcome of the three years of a DNA-based neonatal screening program for glutaric aciduria type I in Manitoba and	<p><u>Study design:</u></p> <p>Prospective follow-up study in Canada, n=4 asymptomatic patients</p> <p><u>Treatment:</u></p> <p>Maintenance treatment: Protein restriction (1.5 g/kg/d),</p>	<ul style="list-style-type: none"> - 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 treatment (personal communication 5 / 5 patients suffered crises, C. R. Greenberg);

	Northwestern Ontario, Canada.	Carnitine (50-100 mg/kg/d), Riboflavin 100 mg/d; b) Emergency treatment; c) Additional treatment: in one child: vitamin E, topiramate <u>Monitoring</u> : "1.5 times maintenance fluid, adequate calories...high dose intravenous carnitine, and pharmacological doses of riboflavin" (no exact protocol specified).	- 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.	<u>Study design</u> : 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.	<u>Study design</u> : - Case report (n=1)	- Subdural hemorrhages in a child with GA-I; discussion on the differential diagnosis of non- accidental 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	<u>Study design</u> : - 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.	<u>Study design</u> : - n=11 patients (9 symptomatic, 2 presymptomatic), - No standard treatment: low-protein diet and/or lysine/tryptophan-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, slight 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: lysine- restricted diet, carnitine supplementation, no tryptophan 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.	<u>Study design</u> : - Case report (n=1 pre-symptomatic patient); lysine/tryptophan-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.	<u>Study design</u> : - 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.	<u>Study design</u> : - 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

<p>Kölker et al (2001) J Pediatr 138: 277-279.</p>	<p>Acute encephalopathy despite early therapy in a patient with homozygosity for E365K in the glutaryl-CoA dehydrogenase gene.</p>	<p><u>Study design:</u> - Case report (n=1), - Turkish boy, diagnosed and treated early (diagnosed due to macrocephaly); - lysine-restricted diet, carnitine and emergency treatment</p>	<p>- Acute encephalopathic crisis despite early treatment with lysine-restricted diet and carnitine (it has been found out later that this family showed a poor compliance, unpublished observation).</p>
<p>Kölker et al (2003) Neuropediatrics ; 34 : 253-260.</p>	<p>Glutaryl-CoA dehydrogenase deficiency: Regional-specific analysis of organic acids and acylcarnitines in post mortem brain predicts vulnerability of the putamen.</p>	<p><u>Study design:</u> - Case report and post mortem examination in one adolescent (age 14 years) with fatal disease course.</p>	<p>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.</p>
<p>Külkens et al (2005) Neurology; 64: 2142-2144.</p>	<p>Late-onset neurologic disease in glutaryl-CoA dehydrogenase deficiency.</p>	<p><u>Study design:</u> 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 glutaric aciduria type I.</p>	<p>Clinical presentation - Severe headaches, gait disturbances (ataxia), tremor, vertigo, hallucinations, 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 edematous swelling of tissue. - Concentrations of glutaric acid (approx. 5,000 µmol/L) and 3-hydroxyglutaric acid (appr. 200 µmol/L) were massively elevated.</p>
<p>Kurul et al (2004) Pediatr Neurol 31: 228-231.</p>	<p>Glutaric aciduria type 1: proton resonance spectroscopy findings.</p>	<p><u>Study design:</u> - Case report (n=1), magnetic resonance spectroscopy</p>	<p>- 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.</p>
<p>Kyllerman and Steen (1980) Arch Pediatr 37; 279.</p>	<p>A "common" metabolic disorder?</p>	<p><u>Study design:</u> Estimation of prevalence in Sweden</p>	<p>- Prevalence of glutaric aciduria type I in Sweden was estimated to 1 in 30,000 newborns.</p>
<p>Kyllerman et al (1994) Mov Disord 9: 22-30 → see also: Bjugstad et al (2000); Kyllerman et al (2004)</p>	<p>Dystonia and dyskinesia in glutaric aciduria type I: Clinical heterogeneity and therapeutic considerations</p>	<p><u>Study design:</u> - 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).</p>	<p>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</p>

			<p>go undetected in the cerebral palsy and mentally retarded child and adult populations)</p> <p>Deaths</p> <ul style="list-style-type: none"> - Two children in state of hyperthermia <p>Feeding problems</p> <ul style="list-style-type: none"> - Carnitine and malnutrition developed in patients with severe dystonia and dysphagia which necessitated replacement therapy and gastrostomy. <p>Neuroradiology</p> <ul style="list-style-type: none"> - CCT/MRI: 7/10 deep bitemporal spaces <p>Neuropsychological testing</p> <ul style="list-style-type: none"> - 8/12 receptive language function superior to expressive language and motor function
Lindner et al (2004) J Inherit Metab Dis 27: 851-859.	Neonatal screening for glutaryl-CoA dehydrogenase deficiency.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - 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 	<ul style="list-style-type: none"> - 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.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - 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. 	<p>Biochemical response</p> <ul style="list-style-type: none"> - 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) <p>Clinical response</p> <ul style="list-style-type: none"> - 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.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Case report (n=3) 	<ul style="list-style-type: none"> - Report on glutaric aciduria type I 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.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Case report (n=2) 	<ul style="list-style-type: none"> - 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.	<p><u>Study design:</u></p> <ul style="list-style-type: none"> - Case report (n=2) 	<ul style="list-style-type: none"> - 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
McClelland et al	Glutaric aciduria type	<u>Study design:</u>	- 6-year-old girl with recurrent epileptic

(2009) Dev Med Child Neurol 51 : 235-239.	1 presenting with epilepsy.	<ul style="list-style-type: none"> - Case report (n=1) of a 6-year-old girl with recurrent epileptic seizures. - First report of a GA-I patient with epileptic seizures as the sole presenting feature of this disease. 	<ul style="list-style-type: none"> seizures. She had no history of encephalopathy and showed no developmental abnormalities. - The EEG was profoundly abnormal with slow background and mixed multifocal and generalized spike-and-wave discharges. - Seizures deteriorated on valproic acid. - The girl has improved on low protein diet, carnitine, levetiracetam, and lamotrigine. - Conclusions: The case report adds to the clinical spectrum of this disorder. <p>Furthermore, it emphasizes the role of metabolic investigation when first- or second-line treatment of epilepsy is unsuccessful.</p>
Mellerio et al (2008) Ultrasound Obstet Gynecol 31 : 712-715.	Prenatal cerebral ultrasound and MRI findings in glutaric aciduria type 1: a de novo case.	<u>Study design:</u> <ul style="list-style-type: none"> - Case report (n=1) - Fetal and postnatal MRI and ultrasound studies. – 	<ul style="list-style-type: none"> - Fetal MRI study in at gestational age 33 weeks showing enlarged Sylvian fissures, multiple bilateral subependymal cysts, diffuse hyperintensity in the periventricular white matter and severe increase of the the supratentorial subarachnoid spaces. Basal ganglia were normal.
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.	<u>Study design:</u> <ul style="list-style-type: none"> - Case report (n=2), phosphorus magnetic resonance spectroscopy 	<ul style="list-style-type: none"> - 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 benefit.
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	<u>Study design:</u> <ul style="list-style-type: none"> - Cohort study in 14 children from the Old Order Amish community in Lancaster County, Pennsylvania. <p>→ See Strauss et al 2003</p>	<p>Clinical course of the disease</p> <ul style="list-style-type: none"> - 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. <p>Treatment options</p> <ul style="list-style-type: none"> - Restriction of dietary protein, limitation of protein catabolism, dehydration, and acidosis during illnesses may prevent the onset of progression of neurologic disease. <p>Pedigree</p> <ul style="list-style-type: none"> - 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.	<u>Study design:</u> <ul style="list-style-type: none"> - Case report (n=1) 	<ul style="list-style-type: none"> - 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.	<u>Study design:</u> <ul style="list-style-type: none"> - Case report (n=1), magnetic resonance spectroscopy (MRS) and diffusion-weighted MRI (DWI) was performed after neurological deterioration (most likely during the chronic stage) 	<ul style="list-style-type: none"> - 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.	<u>Study design:</u> <ul style="list-style-type: none"> - Case report (n=1) 	<ul style="list-style-type: none"> - Suspected late-onset glutaric aciduria type I; 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

			encephalopathic crisis - MRI: Basal ganglia with abnormalities, focal areas of white matter changes.
Rakocevic et al (2004) Stereotact Funct Neurosurg 82: 80-83.	Bilateral pallidotomy for severe dystonia in an 18-month-old child with glutaric aciduria.	<u>Study design:</u> - Case report (n=1) - 18-months-old male (Cherokee Indian) 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).	- Partial improvement of dystonia and reduction of pain (only subjective estimation is given), "more alert and interactive", no purposeful use of hands and arms. - Side effect: Pathological eye findings (right gaze preference, limitation of left horizontal gaze).
Secombe et al (1986) Neurology 36: 264-267. → see also: Bjugstad et al (2000)	L-Carnitine treatment in glutaric aciduria type I.	<u>Study design:</u> - Case report (n=1) - 5-year-old girl (child of non-consanguineous 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 acidemia, type I, missed by newborn screening in an infant with dystonia following promethazine administration.	<u>Study design:</u> - 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	<u>Study design:</u> - 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.	<u>Study design:</u> - 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% - Abnormal 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?	<u>Study design:</u> - Questionnaire-based evaluation (via Metab-I) of current practice of oral L-carnitine supplementation in MCAD	- 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

		<p>deficiency, propionic (PA) and methylmalonic acidurias (MMA); glutaric aciduria type I was only included into the discussion.</p> <p>- Literature review (PubMed): evaluation of evidence levels according to SIGN</p>	<p>orally)</p> <p>- Literature review: Most papers supported use of L-carnitine in PA and MMA, documenting biochemical or clinical improvement; only 5 relevant papers were 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).</p> <p>- Conclusions: Using SIGN criteria, recommendations for oral L-carnitine supplementation in these diseases would only be graded as D (lowest grade).</p>
<p>Walter et al (2009) J Inherit Metab Dis 32 : 95-101.</p>	<p>Bloodspot acylcarnitine and amino acid analysis in cord blood samples: efficacy and reference data from a large cohort study.</p>	<p><u>Study design:</u></p> <p>- Diagnostic study on cord blood samples collected at birth and analysed for acylcarnitine and amino acid profiles by tandem mass spectrometry in two laboratories</p> <p>- One laboratory used butylated derivatives, the other used underivatized samples. The same laboratories performed routine blood spot newborn screening at 5-7 days of age on these babies.</p>	<p>- 24,983 newborns were examined.</p> <p>- No patient with glutaric aciduria type I was identified.</p> <p>- Cord blood testing missed some patients with PKU, MSUD, argininosuccinic aciduria, MMA, GA-II, MCAD deficiency, HMG-CoA lyase deficiency.</p> <p>- Conclusions: cord blood testing is of limited value in detecting inherited metabolic disease. The metabolites associated with most disorders examined were not elevated in cord blood. Some maternal disorders (3-MCC deficiency, carnitine transporter defect) are detected. It can only be extrapolated that for GA-I cord blood might not be advantageous compared to regular newborn screening using dried blood spots.</p>
<p>Woelfle et al (1996) Pediatr Radiol 26 : 779-781.</p> <p>→ see also: Bjugstad et al (2000)</p>	<p>Subdural hematoma and glutaric aciduria type I.</p>	<p><u>Study design:</u></p> <p>- Case report (n=1)</p>	<p>- Bilateral subdural hemorrhages and frontotemporal atrophy; neurosurgical intervention; regression of subdural effusions but deterioration of neurologic disease</p> <p>- Diagnosis was just made after the neurosurgical intervention</p> <p>- Conclusion: GA I should be included into the differential diagnosis of unexplained subdural hematoma and neurological deficits.</p>

Level 4. Expert opinion

Authors	Title	Description	Contents
Baric et al (1998) J Inherit Metab Dis 21 : 326-340.	Diagnosis and management of glutaric aciduria type I.	<u>Review</u> On diagnostic work-up and treatment in glutaric aciduria type I. Based on the presentations and discussions of the 2 nd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Rauischholzhausen, Germany, 1996).	Maintenance 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 (sleepiness, ill temper, irritability, loss of appetite, death) - Dystonia may worsen on high-protein meals et vice versa (anecdotal reports) Emergency treatment: <u>a) Management at home:</u> - 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) <u>b) Management at hospital:</u> - 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), dextrometoprophan (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.	<u>Review:</u> Based on the presentation at the 37 th SSIEM meeting in York, UK (1998)	Maintenance 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.	<u>Review:</u> Based on a presentation and the discussion at the 3 rd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Heidelberg, Germany, 2003).	Outpatient/home emergency treatment: - Recommendations for maltodextran/dextrose, protein intake, and pharmacotherapy Inpatient emergency treatment - 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.	<u>Review:</u> Based on a presentation and the discussion at the 3 rd 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	<u>Review:</u> Based on a presentation and the discussion at the 3 rd 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

			<p>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!).</p> <ul style="list-style-type: none"> - 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 et al (2002) J Inherit Metab Dis 25: 531-546.	Emergency management of inherited metabolic diseases.	<u>Review:</u> 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).	<p>Principles of emergency treatment for "intoxication type":</p> <ul style="list-style-type: none"> - 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.	<u>Review:</u> Report from the 2 nd International Workshop on Glutaryl-CoA Dehydrogenase Deficiency (Rauischholzhausen, Germany, 1996)	<p>Carnitine supplementation:</p> <ul style="list-style-type: none"> - 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 <p>Dietary treatment:</p> <ul style="list-style-type: none"> - 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	<u>Review:</u> Case reports on lysine- and protein (n=14)-restricted patients (n=19); Reference to dietary recommendations for protein and micronutrients	<p>Pharmacological treatment:</p> <ol style="list-style-type: none"> a) Riboflavin: most studies failed to show a positive effect; b) Valproate: inconsistent results; secondary carnitine depletion as severe side effect; c) Carnitine: 100-300 mg/kg/d to normalize plasma levels of free carnitine. <p>Dietary treatment:</p> <ul style="list-style-type: none"> - Biochemical response if lysine intake is 70 mg/kg/d and tryptophan intake is 30 mg/kg/d; correlation between plasma lysine and plasma GA concentrations; - Poor growth and low plasma lysine and tryptophan concentration if intake further decreases (lysine < 50 mg/kg/d, tryptophan < 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. <p>Guidelines for nutrition support:</p> <ol style="list-style-type: none"> a) Maintenance treatment <ul style="list-style-type: none"> - Major goal: Promote normal growth and development (or prevent further neurologic deterioration) by lowering GA in plasma, CSF, and urine while maintaining normal plasma levels of lysine and tryptophan. - 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,

			<p>fish, eggs) is not recommended;</p> <ul style="list-style-type: none">- Energy supply may be higher in handicapped children;- Gastrostomy should be considered if feeding difficulties limit oral feeding; <p>b) Emergency treatment</p> <ul style="list-style-type: none">- Major goal: Inhibit protein catabolism during acute illness;- lysine and tryptophan 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 lysine/tryptophan-free solutions should be administered IV <p>c) Monitoring</p> <ul style="list-style-type: none">- 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
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