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ORIGINAL ARTICLE

Long-term follow-up, neurological outcome and survival rate in 28 Nordic patients with glutaric aciduria type 1

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Summary All 28 patients, 13 females and 15 males, with glutaric aciduria type 1 diagnosed between 1975 and 2001 in Denmark, Finland, Norway and Sweden were identified and studied retrospectively until 2001. Mass screening was not performed. Three were sibling cases. Prenatal enzymatic diagnosis performed in 11 pregnancies led to termination in one. The median follow-up time was 14 years. Six patients had died. At 10 years of age the cumulative survival rate was 89% and at 35 years 44%. The dominating neurological sign was dystonia in 20 and dyskinesia in 4. Three had only slight spastic signs and information was missing in one. The head circumference at birth was significantly larger than normal and increased significantly until 6 months of age. The onset was acute encephalopathic in 24 patients and insidious in 3. From the time of diagnosis, all patients but one were prescribed protein restriction and/or a diet low in lysine and tryptophan. Riboflavine and/or carnitine supplementation were given to 25. Neurological deficits did not improve on the offered treatment. Deterioration may have been averted by intense acute metabolic treatment in a few patients. Dystonia correlated significantly to absence of speech but not to cognitive function. Severe disability, including motor, cognitive and speech functions, correlated significantly with acute onset, dystonia and mortality, and weakly with a deteriorating course, but not with age at onset, diagnosis, or follow-up, nor to head size. Results from future population studies derived from mass screening will have to relate to clinical diagnostic series of the kind presented here.

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Introduction

Glutaric aciduria type 1 (GA1) is an autosomal recessive inborn error of amino acid degradation caused by deficiency of glutaryl-CoA dehydrogenase (GCDH).[1] Deficiency results in the accumulation of glutaric acid, 3-hydroxyglutaric and glutaconic acid in body fluids and tissues detectable in the urine as well as in the cerebrospinal fluid and plasma.[2]

The typical presentation of GA1 is with an acute encephalitis-like metabolic encephalopathy during an intercurrent illness in the first 3 years of life.[3] The mode of onset can also be insidious with gradually progressive symptoms.[4] Damage to the basal ganglia in GA1 is associated with a dominating severe dystonic-dyskinetic disorder, demonstrating choreoathetosis, dystonia and rigidity sometimes mixed with spastic signs.[3,5] Cognitive functions are relatively undisturbed, although speech and motor disabilities may limit accurate assessment.[3] Macrocephaly may appear before or in the absence of any motor deficit. A subgroup of patients are asymptomatic.

The presentation and the neurological impairments of GA1 can be highly variable, even within the same sibship.[6] This makes it difficult to give an accurate prognosis for the individual patient based on biochemical and molecular markers alone. Long-term prognosis, general development and possible later deterioration have not been reported in detail. We therefore conducted a survey of all Scandinavian patients diagnosed clinically before the introduction of mass screening programs.

Material and methods

Included in this study were all cases of GA1, diagnosed between 1975 and 2001 in Denmark, Finland, Norway and Sweden. Ascertainment of diagnosed probands was considered complete based on information from close paediatric networks and collaboration on GA1 within and between the respective countries. Diagnosis was based on the detection of glutaric acid in the urine, confirmed by repeated assays and enzymatic analysis of GCDH. Population screening for inborn organic acidurias was not conducted in any of the included countries during the time.

All cases were diagnosed either on clinical suspicion of metabolic disorder in a sick child ($n = 25$) or on sibling connection ($n = 3$). Prenatal diagnosis based on enzyme assay was performed in 11 pregnancies from 9 families. One affected fetus was detected, and the pregnancy was terminated. The remaining 10 were non-affected and born healthy.

Latest follow-up date was Dec 31, 2001. Twenty-six of 28 identified patients were examined by one of the authors (LS, TL, OS or MK). Information on two of the patients who died at the ages of 2.5 and 3.5 years, respectively, were based on clinical notes and interviews with their parents.

Dystonia was defined as periods of opisthotonus or stiff and twisting posturing of the trunk and/or extremities; dyskinesia as brief involuntary and abnormal movements giving rise to dyscoordination of motor function; and spasticity as increase of muscle tonus with exaggerated tendon reflexes and plantar response with fanning and upgoing of toes and/or sustained foot clonus.

Motor disability was scored as 1 (mild) in the case of no or mild motor dysfunction and no disability in daily life, as 2 (moderate) in the case of mild to moderate motor dysfunction and some, but not limiting disability in daily life, and as 3 (severe) in the case of wheelchair dependency and severe disability in daily life. Cognitive function was judged from data derived from clinical records of development, normal or special school education and formal IQ tests. It was scored as 1 when considered normal, as 2 when intermediate and as 3 when the IQ level was below 70. Speech was scored as 1 when fluent or nearly fluent, as 2 when only single words could be expressed and as 3 when speech was absent. As a measure of outcome, a disability score was developed as the sum of the scores for motor function, cognitive function and speech giving a minimum of three and a maximum of nine.

Occipital head circumference (OFC) was plotted on growth charts for Swedish newborns and children.[7,8] When at least three successive measurements of OFC within the first 3 years were available, the OFC was estimated to the nearest half centimeter at 40 weeks of postconceptual age and at 6, 12 and 18 months of age, respectively, and expressed in standard deviation (SD) scores.

Reports of CT and MRI scans of the head were collected. The investigations had been performed with varying techniques at several centers and pathological findings were classified into temporal/bitemporal cysts or subarachnoidal enlargements and central atrophy. Basal ganglia atrophy was not categorized as such but contained within the group with central atrophy.

Statistical analysis

For the construction of the survival curve, the Kaplan–Meier method was used and for

the correlation analyses, the nonparametric Spearman rank correlation coefficient.

Results

A total of 28 probands, 13 girls and 15 boys born between 1966 and 2000, were identified and studied (Denmark 10, Finland 1, Norway 9, Sweden 8). There were 25 index cases and three sibling cases. One, a sibling to an older index case, was pre-symptomatically diagnosed at the age of 10 days. The other two, diagnosed at 8 and 9 years, were siblings to younger index cases, themselves diagnosed at 4 years and 1 year 9 months, respectively. In calculations of age at diagnosis and diagnostic delay these three siblings were excluded in order to avoid bias.

Outcome measured as disability score and its distribution is shown in Table 1. A strong correlation was found between increasing disability in motor function and speech ($\rho = 0.71$, $p = 0.0002$) and a slight correlation between speech and cognitive function ($\rho = 0.30$, $p = 0.12$). No correlation was found between motor and cognitive function ($\rho = 0.18$, $p = 0.35$).

Dystonia was the dominating neurological sign in 20 patients and dyskinesia in 4. Eighteen of the 24 had additional spasticity, but never as the dominating sign. Three had only mild spastic signs and in one there was no information. A side asymmetry was observed in 11. Attacks of profuse sweating were observed in 13. The dystonia decreased markedly in 7 of 10 patients where percutaneous gastrostomy had been performed concomitantly with improved nutrition and general well being. A significant correlation was found between increasing disability scores and dystonia (Table 2).

The median follow-up time was 14 years, range 9 months to 36 years. Six patients had died at 9 months, 2.5, 3.5, 17, 26 and 28 years of age, respectively. In five of these patients, dystonia was the dominating neurological sign and in one, there was no information. The causes of death comprised severe dystonic periods with fluctuating hyperthermia, profuse sweating and sudden respiratory arrest. There was a strong correlation between high disability scores and death (Table 2).

Life expectancy from birth using the Kaplan–Meier method is shown in Fig. 1. Two children died in close connection to the onset of GA1 disease, one at 2.5 years after onset and three at 16 years or more following long stable periods. At 10 years of age, the cumulative survival rate was estimated to 89% and at 35 years to 44%.

The long-term course was considered unchanged since onset in 16 patients and gradually deteriorating in 12. A second severe crisis leading to death was recorded in one patient. Neurological improvement was not observed in any one. A slight correlation between disability score and course was found, $p = 0.06$ (Table 2).

The onset of GA1 disease was considered acute in 24 patients at a median age of 10 months (range 4 months to 2.5 years). Intercurrent illness preceding the acute onset was documented in 18 patients; infectious agents in 15, poliovirus immunization in 1 and suspicion of cerebral haemorrhage in 2. No triggering event had been documented in 4, and in 2 patients there was no information. The onset was characterized by an acute encephalitis-like condition including sudden unconsciousness and convulsions in 22 and by signs of severe infectious

Table 1 Distribution of disability score in 28 patients with glutaric aciduria type 1 by motor function, cognitive function and speech.

	Disability score						
	3 ($n = 3$)	4 ($n = 1$)	5 ($n = 3$)	6 ($n = 4$)	7 ($n = 6$)	8 ($n = 3$)	9 ($n = 8$)
Motor disability							
Mild, $n = 6$	3	1	1	1			
Moderate, $n = 2$			1	1			
Severe, $n = 20$			1	2	6	3	8
Cognitive function							
Normal, $n = 12$	3	1	2	2	4		
Ambiguous, $n = 4$					2	2	
Not normal, $n = 12$			1	2		1	8
Speech							
Fluent/nearly fluent, $n = 6$	3		2	1			
Single words, $n = 8$		1	1	3	2	1	
No words, $n = 14$					4	2	8

Table 2 Distribution of disability score and correlation with nominal parameters.

	3 ($n = 3$)	4 ($n = 1$)	5 ($n = 3$)	6 ($n = 4$)	7 ($n = 6$)	8 ($n = 3$)	9 ($n = 8$)	ρ	p
Status								0.55	0.004
Alive, $n = 22$	3	1	3	4	6		5		
Death, $n = 6$						3	3		
Neurological status[a]								0.49	0.01
Near normal, $n = 3$	2		1						
Dyskinesia, $n = 4$	0	1		2	0		1		
Dystonia, $n = 20$	1	0	2	2	6	3	6		
Onset								0.63	0,001
Asympomatic, $n = 1$			1						
Subacute, $n = 3$	2	0	1						
Acute infection, $n = 2$		1		1					
Acute encephalopathy, $n = 22$	1		1	3	6	3	8		
Glutaric acid in the urine[b]								0.04	0,85
Low/not detectable, $n = 5$	1			2	1		1		
Moderate, $n = 4$			1		1		2		
High, $n = 19$	2	1	2	4	2	3	5		
Enzyme activity[c]								0.18	0.4
$<3\%$, $n = 20$	3	1	1	3	4	2	6		
$\geq 3\%$, $n = 3$			1	1	1				
Course								0.37	0.06
Unchanged, $n = 16$	3		2	3	4	2	2		
Worse, $n = 12$	0	1	1	1	2	1	6		

[a] Information missing in one.
[b] Low = <100, moderate = 100–1000 and high = >1000 mmol/mol creatinin.
[c] Information missing in five.

disease in 2. The majority had reports of unspecific developmental delay before the acute onset. An insidious onset was considered in 3 patients. All three showed gradually increasing neurological signs starting before 1 year of age. One child was non-symptomatic. There was a strong correlation between acute onset and high disability score, survival and dystonia (Table 2). Acute onset

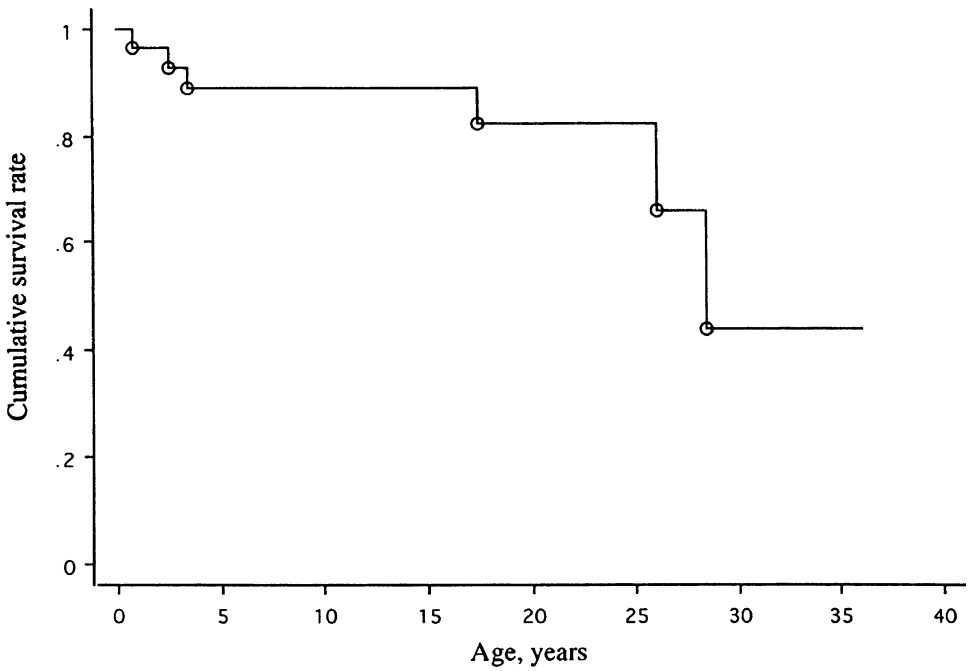

Figure 1 Survival in 28 children with glutaric aciduria type 1.

Table 3 Correlation between disability score and continuous variables.

	Disability score	
	ρ	p-Value
Age at onset	0.04	0.83
Age of diagnosis	0.02	0.91
Age at follow-up	−0.04	0.84
Diagnostic delay	0.03	0.87
OFC		
40 w Postconceptual age	0.02	0.94
6 Months	−0.07	0.76
12 Months	0.04	0.86
18 Months	0.11	0.60

correlated to speech dysfunction ($p = 0.0003$) but not to cognition ($p = 0.35$).

Diagnosis of GA1 in the 25 index cases was made at a median of 1.7 years (range 0.5–15 years). No correlation was found between disability score and age at onset (Table 3). In the 23 with acute onset, the median diagnostic delay, appreciated as the time lag from the first symptoms of GA1 until the appropriate laboratory analyses were performed, was 0.1 years (range 0–14.7 years). In the 2 with insidious onset the diagnostic delay was 2.5 and 9.5 years, respectively. Diagnostic delay against birth year is shown in Fig. 2. The delay decreased during the study period. No significant correlation between disability score and diagnostic delay was found (Table 3).

The glutaric acid level in urine at diagnosis was considered high (>1000 mmol/mol creatinin) in 19 patients, moderate (100–1000) in 4, low (<100) in 4 and was not raised in 1. Subsequently a reduction of glutaric acid excretion in the urine was noted in 13 patients, no change in 7 and an increase in 1. No information was given in six patients. The level of glutarate excretion varied widely even within individual patients. Several reports indicated less attacks of sweating and irritability when excretion levels were low. Treatment of threatening metabolic decompensation with intravenous glucose, buffering and carnitine had been practised in a few cases with reversal of acute disease and stable neurological function. GCDH enzyme activity in fibroblasts was reported in 23, showing levels of <3% of normal in 20, and >3% in 3. No correlation was found between disability score and the level of glutaric acid or enzyme activity (Table 2). The R402W mutation was present in 6 patients and dominated in a scatter of 19 different mutations detected in 21 investigated patients. 12 were homozygotes (including 2 sibling pairs) and 11 compound heterozygotes.

All children but one, who died in close connection to the diagnosis, had from diagnosis been administered low protein diet. Half of them had also been prescribed lysine and tryptophan restriction. Riboflavin and/or carnitine supplementation was given to 25 patients. Signs of neurologic dysfunction before the introduction of dietary therapy were found in 26 of 27 patients.

In the three sibships, the second diagnosed sibling was prescribed diet from the time of diagnosis. One of them was diagnosed at birth.

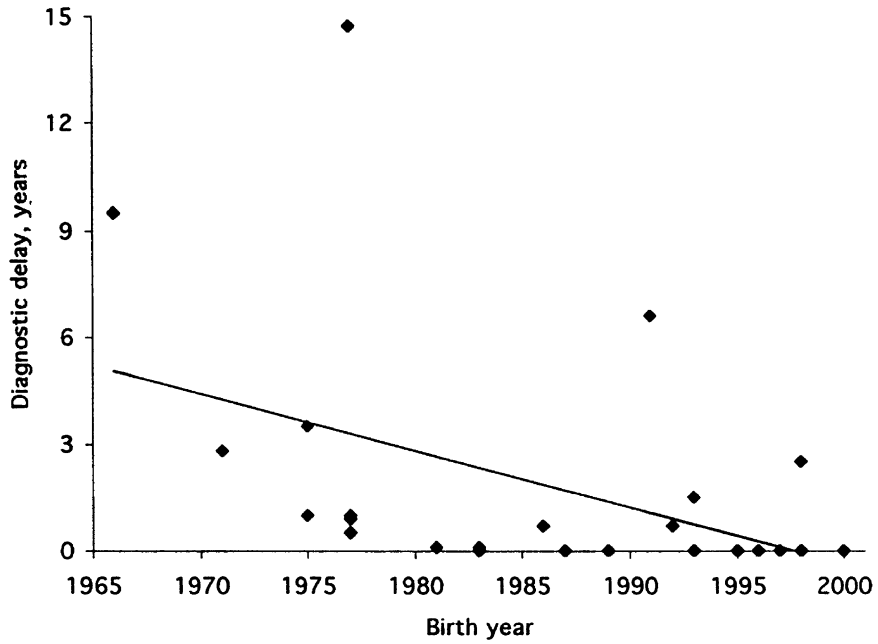

Figure 2 Correlation between diagnostic delay and birth year in 25 index children with glutaric aciduria type 1.

Table 4 Effect of treatment in patients with glutaric aciduria type 1.

	Number of patients treated	Effect	
		Yes	No
Diazepam	16	15	1
Baclofen orally	21	18	3
Baclofen pump	2	2	0
Valproate	9	1	8
Vigabatrine	8	2	6
L-dopa	3	0	3

Initially non-symptomatic, he later developed mild motor dysfunction, mild mental retardation and ADHD (attention deficit hyperactivity disorder). Another with mild spasticity since 2 years of age was diagnosed 6 years later, never had signs of impeding metabolic decompensation and was still normally functioning by 34 years. The third one was diagnosed at 9 years of age. He had had an encephalitis-like disease at 7 months and was severely dystonic since then.

The effect of pharmalogical treatment is shown in Table 4. Peroral diazepam and baclofen was the most common treatment with the best positive effects reported from diazepam. Intrathecal baclofen pump was inserted in two dystonic children with relaxation of the dystonic signs in both.

Pregnancies and deliveries were generally normal. One patient had had a moderate hypoxic-ischaemic encephalopathy with Apgar scores of 2, 4, 6 at 1, 5 and 10 min and early neonatal seizures. Gestational age was known in all but 1, mean 39.7 weeks (range 36–43). Birth weight was known in 26, mean birth weight 3632 g (range 2570–4410). OFC at birth was known in 23, mean 36.7 cm (range 33–40.5). At 40 weeks postconceptual age and 6, 12 and 18 months of age, the mean OFC was significantly larger than normal, $p < 0.001$. No correlation was found between disability score and OFC at any time of measurements (Table 3).

Head growth could be followed in 19 patients (Fig. 3). There was a significant increase from 1.0 SD score above normal at 40 weeks of postconceptual age to 2.2 SD scores at 6 months ($p < 0.0001$), with a slight decrease after that time to 1.7 SD scores at 18 months ($p = 0.07$). Seven patients had been operated on with subdural-peritoneal shunts, five of them at the same center. Shunt insertion had no obvious effect on later head growth.

CT/MRI had been performed in 26 patients. The findings were normal in four patients and in two central atrophy was recorded. The remaining 20 (77%) all had bitemporal enlargements in combination with central atrophy.

Discussion

In GA1 the lack of association between the levels of excreted pathological metabolites and the risk of permanent brain dysfunctions is not easily reconciled with a notion of gradually increasing toxic effects on the brain. Neurologically normal persons may excrete high amounts of glutarate and some with the typical neurological lesions may excrete low amounts and have a comparatively high residual enzyme activity.[9,10] Bergman et al.[5] e.g. reported on the development of acute profound dystonia in three previously normal infants. Two of these patients had excessive urinary excretion of glutaric acid but one did not. Both extremes were encountered in the Nordic patients. The typical onset was

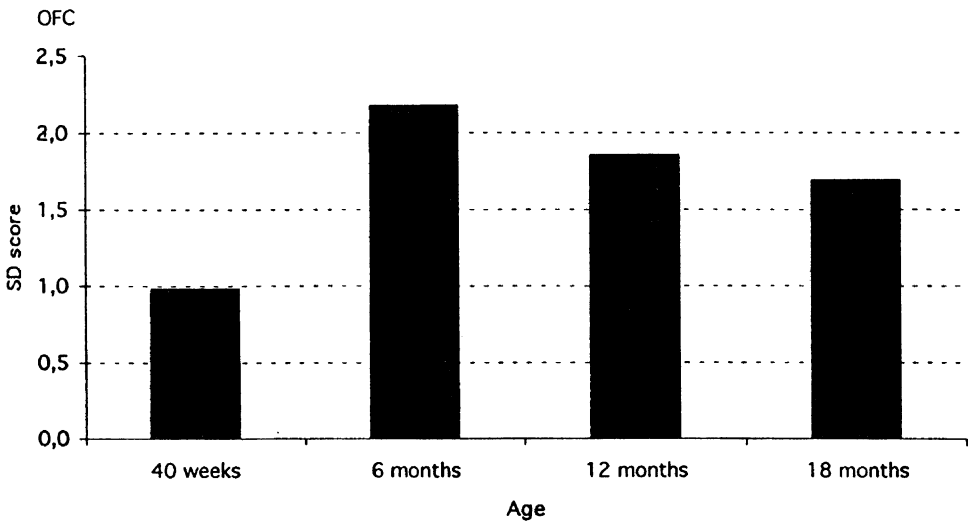

Figure 3 Development of head circumference in 19 children with glutaric aciduria type 1.

an acute metabolic crisis with severe encephalopathy during the first 3 years of life and happened to 24 of the 28 patients in our study before 2.5 years of age. New neurological signs did not occur during the years following the initial event even though the original abnormalities were considered to have become more pronounced in 12. Slow, insidious onset was in our study unusual.

This study showed a significant correlation between acute onset and dominating dystonia but not between acute onset and mental retardation indicating that the basal ganglia and not the cerebral cortex were the prime targets for acute damage. Brain injury sustained on these occasions did not improve by later dietary management. The brain dysfunction in GA1 is typically dominated by extrapyramidal abnormalities and better preserved mental than motor capacities. Dystonia, dyskinesia and probably also oral and speech dysfunctions signify damage to basal ganglia neurons, particularly in the putamen. In one study PET and MRI performed in eight patients showed that the major involvement was localized to putamen and the caudate head. Mild cerebral cortical disturbances cannot be excluded. Reduced fluoro-2-deoxyglucose uptake was noted in the thalami and cerebral cortex without morphological change on MRI.[11]

Data collected on 115 patients from 42 published articles showed that nearly all symptomatic children had the onset before 3 years of age.[12] In patients who did not have a precipitating illness before the first appearance of neurological symptoms there was a correlation between age of onset and the severity of motor impairments. In patients who had a precipitating illness, the age at onset did not predict the outcome. In both groups of patients basal ganglia degeneration, enlargement of frontal-temporal spaces and white matter abnormalities were associated with a poorer outcome.

Acute onset in our series correlated strongly to high disability score, dystonia and dysarthria but not to cognitive function and head circumference supporting the view of a dominating subcortical damage.

Clinically, the sudden and catastrophic onset had the character of a metabolic stroke to the basal ganglia. Deficiency of the GCDH enzyme, which is localized in the mitochondria, may be closely associated with a risk for sudden breakdowns of basic cellular energy metabolism brought on by catabolic events such as general infections and anorexia.[13] Pathogenetic mechanisms of neurodegeneration may involve interaction of 3-OH-glutarate with glutamate receptors to induce energy deprivation which interferes with inhibition of NMDA (*N*-methyl-D-aspartate) receptors.[14] Neuronal damage may be triggered by age- and location-specific overstimulation of NMDA receptor subtypes.[2] Recently the term cerebral organic acid disorders was suggested for a group of disorders lacking general metabolic derangements, such as hypoglycaemia, hyperammonemia and acidosis but characterized by an accumulation of organic acids that share structural similarities with the excitatory amino acid glutamate or have been suggested as neurotransmittors or neuromodulators.[15] Included in this group are aspartoacylase deficiency, GCDH deficiency (GA1), D-2- and L-2-hydroxyglutaric acidurias.

Management of GA1 is based on dietary restriction of tryptophan, lysine and protein, *supplements* with L-carnitine and riboflavine and, during acute deterioration glucose infusion and correction of metabolic acidosis and a catabolic state. While carnitine supplementation is widely accepted there is disagreement and lack of satisfactory data on many other aspects on the management of GA 1 including the use of riboflavin which in the form of flavin adenine dinucleotide acts as cofactor to the GCDH enzyme.[13]

We could not detect any definite beneficial effects from long-term dietary treatment in patients who had already sustained severe brain damages. The effects of preventive and long-term treatment will remain uncertain until more is known of the pathogenesis of the disorder.[16–19a] Three of our patients were siblings, who were all treated from the time when their siblings were diagnosed. One of them, treated from birth, developed a condition compatible with ADHD and had mild mental retardation. Another one was diagnosed and started on treatment at the age of 8 years although he was nearly free from symptoms and is still normally functioning at the age of 34 years. The third one, diagnosed at 9 years, was severely dystonic since the age of 7 months and was still so at 23 years of age. Symptomatically, oral baclofen treatment had limited effects and intrathecal baclophen pump showed promising results in severely dystonic patients.

Patients usually excrete high levels of glutarate in the urine. Over the years an increasing number of patients with GA1 have been recognized who repeatedly excreted only slightly elevated glutarate or even not detectable amounts. This was also observed in our study with low excretion occurring even among severely dystonic probands. Most patients with GA1 have no or very low measurable GCDH enzyme activity. A few patients may have up to 10 or 15% residual function.[9,20] In the Nordic

patients, enzyme levels were, with few exceptions, nil or a few percent of the normal range. Among the three patients with high residual enzyme activity, one excreted high amounts of glutarate, one low and one repeatedly non-detectable amounts.

In 1998, Schwartz et al.[21] reported the identification of 13 novel mutations in the GCDH gene from different European countries and confirmed that there is very little correlation between the genotype and phenotype of GA 1 patients. In European patients the R402W mutation was found to be more common than other, mostly private mutations.[22] Busquets et al.[20] reported on two groups of GA1-patients. The most frequent mutations were A293T and R402W in the group with high glutarate excretion and compound heterozygotes in the group with basal low or absent glutarate excretion. The R402W mutation was prevalent in this series but the A293T mutation was not detected. The occurrence of homozygotes and compound heterozygotes was equally frequent. Two sibling pairs were homozygotes for different mutations.

Death occurred either within a short time after onset or several years later, following long periods of stable neurological dysfunction. Late death was in this series associated with severe dystonic crises and loss of central temperature control seemingly precipitated by infection as also reported by Hauser and Boneh.[23] This potentially life-threatening type of cerebral reaction may also be encountered in patients with basal ganglia and thalamic dysfunction from cerebral palsy,[24] cerebral coning in shunt complications,[25] in near drowning accidents (M. Kyllerman personal observation), and in GA1.[23] The acute situation necessitates intensive care with high intravenous fluid administration, sedation, body temperature management and relief of dystonic spasms.

Future studies based on cases diagnosed by population screening procedures[19b] may offer new insights into the prevalence and the clinical spectrum of GA1. Results of preventive treatment efforts in non-symptomatic glutarate excretors will be judged against the results from retrospective long-term studies.

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References

1. Goodman S, Markey SP, Moe PG, Miles BS, Teng CC. Glutaric aciduria a 'new' disorder of amino acid metabolism. *Biochem Med* 1975;**12**:12—21.
2. Hoffmann GF, Zschocke J. Glutaric aciduria type 1: from clinical, biochemical and molecular diversity to successful therapy. *J Inher Metab Dis* 1999;**22**:381—91.
3. Kyllerman M, Skjeldal HO, Lundberg M, et al. Dystonia and dyskinesia in glutaric aciduria type 1: clinical heterogeneity and therapeutic considerations. *Mov disord* 1994;**9**:22—30.
4. Hoffmann GF, Athanassopoulos S, Burlina AB, et al. Clinical course, early diagnosis, treatment and prevention of disease in glutaryl-CoA dehydrogenase deficiency. *Neuropediatrics* 1996;**27**:115—23.
5. Bergman I, Finegold D, Gartner C, et al. Acute profound dystonia in infants with glutaric acidemia. *Pediatrics* 1989; **83**:228—34.
6. Morton HD, Bennett MJ, Seargeant LE, Nichter CA, Kelley IK. Glutaric aciduria type 1: a common cause of episodic encephalopathy and spastic paralysis in the Amish of Lancaster county, Pennsylvania. *Am J Med Genet* 1991;**41**: 89—95.
7. Niklasson A, Ericson A, Fryer JG, et al. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977—1981). *Acta Paediatr Scand* 1991;**80**:756—62.
8. Albertsson-Wikland K, Luo ZC, Niklasson A, Karlberg J. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. *Acta Paediatr* 2002;**91**:739—54.
9. Christensen E, Ribes A, Busquets C, et al. Compound heterozygosity in the glutaryl-CoA dehydrogenase gene with R227P mutation in one allele is associated with no or very low free glutarate excretion. *J Inher Metab Dis* 1997; **20**:383—6.
10. Pineda M, Ribes A, Busquets C, et al. Glutaric aciduria type 1 with high residual glutaryl-CoA dehydrogenase activity. *Dev Med Child Neurol* 1998;**40**:840—2.
11. Al-Essa M, Bakheet S, Patay Z, et al. Fluoro-2-deoxyglucose (18FDG) PET scan of the brain in glutaric aciduria type 1: clinical and MRI correlations. *Brain Dev* 1998;**20**:295—301.
12. Bjugstad KB, Goodman SI, Freed CR. Age at symptom onset predicts severity of motor impairment and clinical outcome of glutaric aciduria type 1. *J Pediatr* 2000;**137**:681—6.
13. Baric I, Zschocke J, Christensen E, et al. Diagnosis and management of glutaric aciduria type 1. *J Inher Metab Dis* 1998;**21**:326—40.
14. Ullrich K, Flott-Rahmel B, Schluff P, et al. Glutaric aciduria type I: pathomechanisms of neurodegeneration. *J Inherit Metab Dis* 1999;**22**:392—403.
15. Kölker S, Mayatepek E, Hoffmann GF. White matter disease in cerebral organic disorders: clinical implications and suggested pathomechanisms. *Neuropediatrics* 2002;**33**: 225—31.
16. Greenberg CR, Prasad AN, Dilling LA, et al. Outcome of the first 3-years of a DNA-based neonatal screening program for glutaric aciduria type I in Manitoba and Northwestern Ontario, Canada. *Mol Genet Metab* 2002;**75**:70—8.
17. Kölker S, Ramaekers V, Zschocke J, Hoffman GF. Acute encephalopathy despite early therapy in a patient with homozygosity for E365K in the glutaryl-coenzyme A dehydrogenase gene. *J Pediatr* 2001;**138**:277—9.
18. Monavari AA, Naughton ER. Prevention of cerebral palsy in glutaric aciduria type 1 by dietary management. *Arch Dis Child* 2000;**82**:67—70.

19(a) Superti-Furga A. Hoffmann GF., Glutaric aciduria type 1 (glutaryl-CoA-dehydrogenase deficiency): advances and unanswered questions. Report from an international meeting. *Eur J Pediatr* 1997;**156**:821—8.

19(b) Superti-Furga A. Glutaric aciduria type 1 and neonatal screening: time to proceed—with caution. *Eur J Pediatr* 2003;**162**(Suppl. 1):S17—S20.

20. Busquets C, Merinero B, Christensen E, et al. Glutaryl-CoA dehydrogensase (GCDH) deficiency in Spain: evidence of two groups of patients, genetically and biochemically distinct. *Pediatr Res* 2000;**48**:315—22.
21. Schwarz M, Christensen E, Superti-Furga A, Brandt NJ. The human glutaryl-CoA dehydrogenase gene: report of intronic sequences and of 13 novel mutations causing glutaric aciduria type 1. *Hum Genet* 1998;**102**:452—8.
22. Zschocke J, Quak E, Guldberg P, Hoffmann GF. Mutation analysis in glutaric aciduria type 1. *J Med Genet* 2000;**37**: 177—81.
23. Hauser SE, Boneh A. Severe clinical course with recurrent hyperpyrexia in a patient with glutaric aciduria type 1. *Neuropediatrics* 1999;**30**:51—2.
24. Hagberg B. Emotionally released hyperthermia in cerebral palsy. *Neuropädiatrie* 1970;**3**:295—306.
25. Emanuelson I, von Wendt L, Kyllerman M. Clinical outcome after near-fatal late shunt complication in hydrocephalus. *Childs Nerv Syst* 1994;**10**:270—4.