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Glutaric Acidemia Type 1

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Abstract

Glutaric acidemias comprise different disorders resulting in an increased urinary excretion of glutaric acid. Glutaric acidemia type 1 (GA-1) is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan metabolism caused by deficiency of glutaryl-CoA dehydrogenase. It results in the accumulation of 3-hydroxyglutaric and glutaric acid. Affected patients can present with brain atrophy and macrocephaly and with acute dystonia secondary to striatal degeneration in most cases triggered by an intercurrent childhood infection with fever between 6 and 18 months of age. This disorder can be identified by increased glutaryl (C5DC) carnitine on newborn screening. Urine organic acid analysis indicates the presence of excess 3-OH-glutaric acid, and urine acylcarnitine profile shows glutaryl carnitine as the major peak. Therapy consists in carnitine supplementation to remove glutaric acid, a diet restricted in amino acids capable of producing glutaric acid, and prompt treatment of intercurrent illnesses. Early diagnosis and therapy reduce the risk of acute dystonia in patients with GA-1.

Keywords

glutaric acidemia; macrocephaly; dystonia; striatal degeneration

INTRODUCTION

Glutaric acidemia type 1 (GA-1, OMIM 231670) is an autosomal recessive inborn error of lysine, hydroxylisine, and tryptophan metabolism caused by deficiency of glutaryl-CoA dehydrogenase (EC 1.3.99.7). This enzyme, located in the mitochondrial matrix, converts glutaryl-CoA to crotonyl-CoA. Glutaric acidemia type 1 was first reported in 1975 by Goodman et al [Goodman et al., 1975] and is characterized by macrocephaly at birth or shortly after, dystonia, many times resembling seizures at the first episode, with degeneration of the caudate and the putamen. Since the initial description, more than 200 cases were subsequently reported including 77 patients from a single center [Strauss and Morton, 2003; Strauss et al., 2003]. This disorder can be diagnosed by expanded newborn screening by MS/MS and here we will review what can be expected from early diagnosis as compared to clinical diagnosis.

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GENETIC BASIS

GA-1 is caused by heterogenous mutations in the glutaryl-CoA dehydrogenase gene. The gene spans about 7 kb on chromosome 19p13.2 and is composed of 11 exons [Goodman et al., 1998]. More than 63 different mutations, including missense, nonsense and intronic variants, have been reported in patients with GA-1. The most common mutation is R402W in exon 10 that accounts for less than 20% of mutations [Goodman et al., 1998]. The R402W missense mutation retains only about 3% enzyme activity while other missense mutations (such as A421V in exon 11) retain significant residual enzyme activity (up to about 40% of normal) when expressed in *Escherichia coli* [Goodman et al., 1998]. It is unclear whether individuals with "leaky" mutations (such as A421V, prevalent in the old-order Amish of Pennsylvania) have an increased probability of remaining asymptomatic, i.e. not having striato-nigral degeneration.

There is correlation between residual enzyme activity and biochemical phenotype, i.e. urinary excretion of glutaric acid. Patients with a mild mutation (such as R227P and V400M) on at least one chromosome might have low or normal urinary excretion of glutaric acid [Pineda et al., 1998]. By contrast, patients with severe mutations such as R402W or A293T on both alleles have no residual activity and show the typical urinary metabolite pattern [Christensen et al., 2004]. However, there is no association between phenotype and severity of the genetic lesion [Christensen et al., 2004], since siblings within the same family and with the same mutation and genetic background can have discordant phenotypes. In addition, patients with different mutations and very different biochemical phenotype (urinary excretion of glutaric and 3-OH-glutaric acid) can presents similarly. Therefore, non-genetic factors, among which fever, infections and fasting, play an important role in precipitating neuronal damage in glutaric acidemia type 1.

The combined worldwide frequency of GA-1 based on newborn screening by MS/MS of 2.5 million children is 1:100,000 infants [Lindner et al., 2004]. The disorder is very frequent (up to 1:300) among certain ethnic groups such as the Old-Order Amish community of Pennsylvania [Morton et al., 1991] and the North American Ojibway-Cree in Canada [Greenberg et al., 1995; Haworth et al., 1991]. In Sweden, it affects 1:30,000 newborn [Kyllerman and Steen, 1980] and about 1:50,000 in the USA [Goodman, 2001].

Patients with glutaric acidemia type 1 are more vulnerable to striatal damage resulting in a severe dystonic movement disorder between 6 and 18 months of age [Strauss et al., 2003]. It is still unclear what causes this selective sensitivity. Glutaric and 3-OH-glutaric acid accumulate in the brain of affected individuals, even in patients who are low excretors of glutaric acid [Funk et al., 2005], at levels that are one or two orders of magnitude higher than in other tissues [Funk et al., 2005]. Glutaric acid and 3-OH glutaric acid accumulation leads to neuronal damage with loss of striatal neuron at time of sepsis/fever [Funk et al., 2005]. This might be followed or accompanied to lymphocytic infiltration and subsequently by glial proliferation followed by atrophy. Neuronal loss happens at time of the acute event and does not progress over time [Funk et al., 2005]. Involvement of the striatum might be due to their abundance of receptors for glutamate. Among these, the N-methyl-D-aspartate receptor seems to play a major role in excitotoxicity mediated by 3-OH-glutaric acid [Kolker et al., 2004b] or by quinolinic acid [Varadkar and Surtees, 2004]. Neuronal damage can be aggravated by production of cytokines and nitric oxide [Kolker et al., 2004b]. Abnormalities of the development of blood vessels or of blood flow could contribute to striatal injury [Funk et al., 2005; Muhlhausen et al., 2004a].

A mouse model for glutaric acidemia type 1 was recently developed via targeted deletion of the glutaryl CoA dehydrogenase gene in embryonic stem cells [Koeller et al., 2002]. Mutant

mice had a biochemical phenotype very similar to human patients with glutaric acidemia type 1, including elevations of glutaric and 3-OH-glutaric acid. However, they did not present the complex clinical phenotype of humans with glutaric acidemia type 1. Affected mice had a mild motor deficit but did not develop the progressive dystonia seen in human patients, even after subjecting them to metabolic stress [Koeller et al., 2002]. Mutant mice had a diffuse spongiform myelinopathy similar to that seen in GA-I patients, but no striatal degeneration [Koeller et al., 2002]. Intrinsic differences between the striata of mice and men have been proposed to explain this fundamental difference [Koeller et al., 2002].

CLINICAL MANIFESTATIONS

The clinical manifestations of GA-1 can vary considerably even between siblings, suggesting an important environmental component. Most patients have macrocephaly at birth or develop it shortly thereafter. Most of these patients have no clinical symptoms beyond a large head. One of our patients had a sudden post-natal increase in head circumference that prompted diagnosis at 11 months of age. Brain imaging performed shortly after birth usually shows the appearance of fronto-parietal brain atrophy with widening of the Sylvian fissures and sometimes arachnoid cysts. This reflects abnormal brain growth during intrauterine life and is therefore hypoplasia rather than atrophy. The reduced amount of brain tissue within an enlarged head has been called micrencephalic macrocephaly [Strauss et al., 2003]. Veins can stretch in the enlarged collection of CSF and are subject to rupture with acute subdural hemorrhages, sometimes following minor head trauma. In some cases, these are accompanied to retinal hemorrhages, raising suspicion of child abuse [Kafil-Hussain et al., 2000].

Acute neurological deterioration happens most frequently between 6 and 18 months of age. This can occur acutely usually triggered by a febrile illness with some degree of dehydration or more insidiously, without a well defined triggering event. Following 1-3 days of fever and usually vomiting, children become acutely hypotonic, lose head control, and can have abnormal movements similar to seizures (although, in children identified at our center, electroencephalograms failed to detect seizure activity). Hypotonia then slowly (weeks) improves and is first alternated then substituted by rigidity and dystonia. Patients may have tongue thrusting with decreased coordination of swallowing, impairing their ability to eat. Some children have partial reversal of these symptoms and become able to eat by mouth adequately. Patients not regaining sufficient swallow coordination require placement of a nasogastric tube first and then a permanent gastrotomy tube/button for feeding with a simultaneous Nissen fonduplication if there are concerns for aspiration. Patients remain severely disabled and will not able to walk. Several patients survive to adult life remaining wheel-chair bound and requiring constant assistance. These patients seem to have relatively normal cognition, respond to commands, but have trouble talking or performing tasks because of poor muscle coordination and severe spasticity.

Laboratory abnormalities commonly detected at time of acute attacks include hypoglycemia, ketonuria, and metabolic acidosis with mild to moderate decrease of bicarbonate levels. Some patients have chronically reduced bicarbonate levels while perfectly compensated. Plasma free carnitine levels are usually mildly to severely reduced at time of presentation.

Acute decompensation has not been reported in patients past five years of age. Many of these children have brain atrophy by MRI and in some cases abnormal myelination, but function very well. Patients escaping acute childhood striatal necrosis do generally well, although recently a 19-year-old female was identified with leukoencephalopathy after presenting with recurrent headaches and oculomotor symptoms [Bahr et al., 2002]. In this

patient, the intensity and severity of headaches improved after diagnosis and initiation of carnitine supplements [Bahr et al., 2002].

DIAGNOSIS

Glutaric acidemia type 1 can be suspected based on clinical presentation or neuroradiology findings. The typical widening of Sylvian fissures with micrencephalic macrocephaly is suggestive of glutaric acidemia type 1.

Medical Imaging

At birth and in infancy, cranial sonography can demonstrate the presence of bilateral cyst-like dilatation of the Sylvian fissures (Fig. 1) [Forstner et al., 1999]. Computerized Tomography (CT) can show early frontotemporal atrophy manifest by enlarged pretemporal subarachnoid spaces (Fig. 2A), with the Sylvian fissures often showing a “batwing” configuration (Fig. 2B) [Brismar and Ozand, 1995]. Other CT findings in glutaric acidemia type I include: hypoattenuation of the lentiform nuclei (caudate and putamen) (Fig. 2C); cerebral hemispheric white matter hypoattenuation, ventricular dilatation, generalized cerebral atrophy, and communicating hydrocephalus [Mandel et al., 1991;Yager et al., 1988]. The subdural hygroma or subdural hemorrhage of glutaric acidemia type 1 may trigger an evaluation for child abuse (Fig. 2D) [Woelfle et al., 1996]. The key to correct diagnosis is the recognition of other imaging characteristics of glutaric acidemia type 1 such as brain atrophy with enlarged Sylvian fissures, lentiform nuclei hypodensity, or white matter hypointensity (Figs. 2A, 2B, 2C).

Magnetic resonance imaging (MRI) of the brain is the modality of choice to investigate children with possible GA-1. Atrophy or hypoplasia of the frontotemporal regions of the cerebral hemispheres, enlarged pretemporal middle cranial fossa subarachnoid spaces, and cyst-like dilatation of the Sylvian fissures are often early findings in glutaric acidemia type I (Fig. 3A) with “batwing” or “box-like” fissures (Fig. 3B) [Neumaier-Probst et al., 2004]. After an acute event of decompensation or following a chronic course, neurotoxicity of the basal ganglia, particularly the putamen and caudate nuclei (lentiform nuclei) becomes evident. During the acute episode, edema within the putamen and caudate are manifest by increased signal intensity on T2 weighted imaging (Fig. 3C) [Desai et al., 2003]. Diffusion restriction reflects cytotoxic edema and disturbed oxidative metabolism (Fig. 3D). With time, neuronal loss and astrogliosis lead to atrophy of the putamen and caudate nucleus leaving persistent T2 hyperintensity (Fig. 3E). Additional findings include hyperintense signal on T2 weighted images involving the dentate nuclei and cerebral hemispheric white matter. These white matter signal changes reflect the combination of neurotoxic effects of metabolic byproducts and dysmyelination and/or demyelination. As the disease progresses, generalized cerebral atrophy, ventricular dilatation, and basal ganglia atrophy become more conspicuous. Subdural hygromas and subdural hemorrhages may accompany cerebral atrophy. Cerebral atrophy, physiologic inertial cerebral forces, and tearing of bridging veins represent the most likely mechanism for the development of these collections. Alternatively, tears or fenestrations in the arachnoid membrane can lead to fluid accumulation within the subdural space (Fig. 3F).

Magnetic resonance spectroscopy (MRS) provides a noninvasive technique to observe certain neural metabolites in vivo. The presence of lactate particularly within the basal ganglia is an indirect index of impaired cerebral oxidative metabolism. Elevation of choline suggests cell membrane turn over which derives from neuronal loss and demyelination. The decline of N-acetylaspartate (NAA) reflects a combination of neuronal volume loss and neuronal dysfunction secondary to the presence of neurotoxic metabolic byproducts. No

consistent abnormalities in magnetic resonance spectroscopy have been identified in patients with glutaric acidemia type 1 [Bodamer et al., 2004].

Biochemical Studies

With urine organic acid analysis, 3-OH-glutaric acid is the diagnostic metabolite (Fig. 4). Glutaconic acid might be present in some patients during acute attacks, together with ketone bodies (Fig. 4A). In the classic patient, glutaric acid remains very elevated even when there is no catabolic state (Fig. 4B). Glutaric acid can be completely normal in some patients (Fig. 4C), but 3-OH-glutaric acid is always present. 3-OH-glutaric acid can be hard to identify since its coelutes with 2-OH-glutaric acid and can be present only in minimal amounts (Fig. 4C).

Glutaric acidemia type 1 produces carnitine deficiency and increases levels of C5 dicarboxylic (glutaryl) carnitine in urine and plasma (Fig. 5). This has been used for neonatal screening using age-adjusted cut-offs. Unfortunately, plasma glutarylcarnitine can be normal in patients with glutaric acidemia type I without an elevation of urine glutaric acid. These rare patients can be missed by newborn screening with MS/MS [Gallagher et al., 2005]. More recently, glutarylcarnitine has been found to be markedly elevated in the urine of patients with GA-1 and virtually diagnostic of this condition (Fig. 5A) [Tortorelli et al., 2005]. Even with this method, some of the rare patients excreting only 3-OH-glutaric, but not glutaric acid in urine can have a normal urine acylcarnitine profile.

Enzyme assay in cultured fibroblasts should be used for definitive confirmation of glutaric acidemia type 1. DNA analysis can also be used, but the lack of a common mutation requires sequencing of the full gene.

Other disorders in which the urinary excretion of glutaric acid is increased are glutaric acidemia type 2 (usually with several other abnormal metabolites and increased 2-OH-glutaric acid, Fig. 6A), glutaric acidemia type 3 (where it can be relatively elevated, but without 3-OH-glutaric acid and with normal plasma and urine acylcarnitine profile, Fig. 6B), alpha-aminoadipic acidemia (with other abnormal metabolites), short-gut syndrome and intestinal infections (without 3-OH-glutaric acid).

Glutaric acidemia type 2 (GA-2) or multiple acyl-CoA dehydrogenase deficiency (MADD) is disorder of mitochondrial fatty and organic acid metabolism caused by mutations in the genes encoding the alpha or beta subunit of electron transfer flavoprotein (ETF) or ETF ubiquinone oxidoreductase (ETFQO) [Frerman and Goodman 1985]. Affected patients can present at birth with (type 1) or without (type 2) congenital anomalies or later in life (type 3) [Loehr et al., 1990]. All three forms of glutaric acidemia type 2 can results in a severe outcome and premature death. These different clinical forms are explained by different ETF/ETFQO mutations leaving different residual activity, with homozygosity for null alleles being associated with abnormal fetal development and congenital anomalies and higher residual enzyme activity observed in patients with type 3 disease [Olsen et al., 2003]. The neonatal-onset forms (type 1 and 2) are usually fatal and are characterized by dysmorphic features with multiorgan abnormalities (type 1 only), nonketotic hypoglycemia, metabolic acidosis, multisystem involvement, and excretion of large amounts of abnormal fatty acid and organic acid metabolites. Late-onset glutaric acidemia type 2 is much more variable in presentation. Patients can have recurrent episodes of lethargy, vomiting, hypoglycemia, metabolic acidosis, and hepatomegaly often triggered by fever, infection or fasting. Some patients have predominant muscular involvement with pain, weakness, and lipid storage myopathy [Loehr et al., 1990]. Urine organic acids in patients with the late onset form of MADD can be intermittently normal and become abnormal only during illnesses or stress. Urine organic acid analysis shows a characteristic profile in all patients with the neonatal

presentation (Fig. 6A), with elevated isovaleric, lactic and pyruvic, ethylmalonic, glutaric, 2-OH-glutaric, and dicarboxylic acids, reflecting impairment of multiple dehydrogenases. Diagnosis is confirmed by measurement of fatty acid oxidation in fibroblasts or direct assay of Electron Transfer Flavoproteins by immunoblot. Free carnitine can be reduced and plasma acylcarnitine analysis by MS/MS can identify patients with MADD. The acylcarnitine profile shows increase in glutaryl carnitine and other acylcarnitines reflecting the impairment of multiple dehydrogenases. At least two patients have been diagnosed through newborn screening programs [Abdenur et al., 2001] and at least one pre-symptomatically identified infant has had normal growth and development so far [Abdenur et al., 2001]. Although patients with the neonatal types of MADD might become symptomatic or die before the results of newborn screening are available, patients with the late-onset variety can benefit from a timely diagnosis. For the other group of patients, the benefit of a diagnosis might also be helpful to the family. Prenatal diagnosis is available for GA-2 [Olsen et al., 2005].

Glutaric acidemia type 3 is possibly by peroxisomal glutaryl-CoA oxidase deficiency [Knerr et al., 2002]. No consistent phenotype has been reported in this condition and is presumable a benign variants. Urine organic acids show a persistent elevation in the excretion of glutaric acid with no other abnormal metabolites (3-OH-glutaric or 2-OH-glutaric acid, Fig. 6B) suggestive of glutaric acidemia type I or II. Plasma and urine acylcarnitine profiles are completely normal in these patients.

NEWBORN SCREENING AND EFFECT OF THERAPY

Newborn screening can identify patients with elevated glutarylcarnitine (C5 dicarboxylic carnitine) [Lindner et al., 2004]. Rare patients excreting normal or only minimally elevated levels of glutaric acid might have normal levels of glutarylcarnitine in blood spots and might be missed by newborn screening [Lindner et al., 2004]. Analysis of urinary acylcarnitine has been proposed as a more sensitive system for their identification [Tortorelli et al., 2005]. Low excretors of glutaric acid can also be identified by DNA-based screening in defined populations with high prevalence of this disorder [Lindner et al., 2004]. Abnormal newborn screening results need to be confirmed by urine organic acid analysis with subsequent enzyme assay and/or mutation identification for definitive confirmation.

In the patients identified so far by newborn screening, neurological damage was prevented in 51/65 patients [Kolker et al., 2004a]. Neurological decompensation was more frequent among Ojibway-Cree Indians [Greenberg et al., 2002] and Old-Order Amish patients [Strauss et al., 2003] as compared to the remaining European and North American patients [Hoffmann et al., 1996; Kolker et al., 2004a; Naughten et al., 2004], in all of whom acute striatal damage was associated with delayed or improper treatment of the acute episode [Kolker et al., 2004a]. Therefore, early identification is only the first step in preventing the acute neurological deterioration associated with glutaric acidemia type 1. Appropriate treatment and emergency plans need to be in place to minimize the risk of adverse neurological outcome. Several different protocols are used in different centers, including low protein diet, diet restricted in lysine/tryptophan, supplementation with carnitine/riboflavin, chronic anticonvulsivant treatment to reduce risk of neuronal damage [Kolker et al., 2004a; Muhlhausen et al., 2004b]. In reviewing the limited experience accumulated so far, a better outcome was obtained with a low-protein diet supplemented with lysine-free special formulas enriched in micronutrients as compared to protein restriction alone [Kolker et al., 2004a]. Chronic anticonvulsivant (topiramate or phenobarnital) use seems of no benefit [Kolker et al., 2004a], while carnitine supplements are used universally and sometimes as the only treatment [Naughten et al., 2004]. Most centers do not use riboflavin, beyond that present in fortified formulas.

In our clinic, we use protein restriction supplemented with lysine-free special formulas and carnitine (100 mg/kd/day) supplements. We monitor growth and development, plasma amino acids to keep all amino acids in the normal range and lysine at or slightly below the normal range (60-90 micromolar). Tryptrophan, another precursor of glutaric acid, gives very variable readings when analyzed in plasma possibly due to its unstability and its levels are not used for dietary adjustments. Despite mildly decreased lysine levels, our patients have shown completely normal growth and development. Levels of free carnitine are kept in the high or slightly above the normal range (60-100 micromolar), to provide a buffer to aid the elimination of glutaric acids in case of acute decompensation. We do not use chronic anticonvulsivants or riboflavin.

All patients' caretakers are instructed about the disease and to bring the child to immediate medical attention at a pediatric medical center in case of fever or inability to eat. There is no substitute for an intelligent assessment by the parents on when to bring the child in. In general, fever, vomiting, or diarrhea lasting more that 12 h should at least result in a phone call to the metabolic specialist. If they are severe or unlikely to resolve in a short time, medical evaluation should be obtained promptly. Parents are provided with an emergency letter explaining the diagnosis, the nature of the disease, contact information for a metabolic specialist on call and listing the immediate management to be started immediately as the child enters an emergency room. The goal of the emergency management is to reverse the catabolic state and enable the child to eat. This can be accomplished by giving intravenous fluids consisting of glucose 10%, ¼-1/2 normal saline (37.5-75 mEq/L NaCl) depending on the child's age, KCl 20 mEq/L at one and one half to two times the physiologic fluid requirements spaced over 24 hours. This should be supplemented by Intralipids (20%) infused at a rate that is 1/10 of the rate of IV fluids. If glucose increases above 180 mg/dL (10 mM), insulin should be started with a bolus of 0.1 U/kg followed by the same dose every hour monitoring glucose and electrolytes and suspending insulin when glucose is <120 mg/dL. Carnitine is given intravenously at 50 mg/kg per dose every 6 hours. Fever should be reduced below 38.5 C using ibuprofen (10 mg/kg per dose repeated every 6-8 hours). A search for the cause of fever and empiric treatment of infections should be initiated if indicated. Oral feeding should be started when tolerated, sometimes with a nasogastric tube, and increased gradually to fully replace intravenous fluids.

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REFERENCES

Abdenur JE, Chamoles NA, Schenone AB, Jorge L, Guinle A, Bernard C, Levandovskiy V, Fusta M, Lavorgna S. Multiple acyl-CoA-dehydrogenase deficiency (MADD): use of acylcarnitines and fatty acids to monitor the response to dietary treatment. Pediatr Res. 2001; 50:61–66. [PubMed: 11420420]

Bahr O, Mader I, Zschocke J, Dichgans J, Schulz JB. Adult onset glutaric aciduria type I presenting with a leukoencephalopathy. Neurology. 2002; 59:1802–1804. [PubMed: 12473778]

Bodamer OA, Gruber S, Stockler-Ipsiroglu S. Nuclear magnetic resonance spectroscopy in glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004; 27:877–883. [PubMed: 15505395]

Brismar J, Ozand PT. CT and MR of the brain in glutaric acidemia type I: a review of 59 published cases and a report of 5 new patients. AJNR Am J Neuroradiol. 1995; 16:675–683. [PubMed: 7611022]

Christensen E, Ribes A, Merinero B, Zschocke J. Correlation of genotype and phenotype in glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004; 27:861–868. [PubMed: 15505393]

Desai NK, Runge VM, Crisp DE, Crisp MB, Naul LG. Magnetic resonance imaging of the brain in glutaric acidemia type I: a review of the literature and a report of four new cases with attention to the basal ganglia and imaging technique. Invest Radiol. 2003; 38:489–496. [PubMed: 12874515]

Forstner R, Hoffmann GF, Gassner I, Heideman P, De Klerk JB, Lawrenz-Wolf B, Doringer E, Weiss-Wichert P, Troger J, Colombo JP, Plochl E. Glutaric aciduria type I: ultrasonographic demonstration of early signs. Pediatr Radiol. 1999; 29:138–143. [PubMed: 9933336]

Frerman FE, Goodman SI. Deficiency of electron transfer flavoprotein or electron transfer flavoprotein:ubiquinone oxidoreductase in glutaric acidemia type II fibroblasts. Proc Natl Acad Sci U S A. 1985; 82:4517–4520. [PubMed: 2989828]

Funk CB, Prasad AN, Frosk P, Sauer S, Kolker S, Greenberg CR, Bigio MR Del. Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. Brain. 2005; 128(Pt 4): 711–722. [PubMed: 15689364]

Gallagher RC, Cowan TM, Goodman SI, Enns GM. Glutaryl-CoA dehydrogenase deficiency and newborn screening: Retrospective analysis of a low excretor provides further evidence that some cases may be missed. Mol Genet Metab. 2005; 86:417–420. [PubMed: 16183314]

Goodman, SI.; Frerman, FE. Organic acidemias due to defects in lysine oxidation: 2-ketoadipic acidemia and glutaric acidemia. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D., editors. McGraw Hill; New York: 2001. p. 2195-2204.

Goodman SI, Markey SP, Moe PG, Miles BS, Teng CC. Glutaric aciduria; a “new” disorder of amino acid metabolism. Biochem Med. 1975; 12:12–21. [PubMed: 1137568]

Goodman SI, Stein DE, Schlesinger S, Christensen E, Schwartz M, Greenberg CR, Elpeleg ON. Glutaryl-CoA dehydrogenase mutations in glutaric acidemia (type I): review and report of thirty novel mutations. Hum Mutat. 1998; 12:141–144. [PubMed: 9711871]

Greenberg CR, Prasad AN, Dilling LA, Thompson JR, Haworth JC, Martin B, Wood-Steiman P, Seargeant LE, Seifert B, Booth FA, Prasad C. Outcome of the first 3-years of a DNA-based neonatal screening program for glutaric acidemia type 1 in Manitoba and northwestern Ontario, Canada. Mol Genet Metab. 2002; 75:70–78. [PubMed: 11825066]

Greenberg CR, Reimer D, Singal R, Triggs-Raine B, Chudley AE, Dilling LA, Philipps S, Haworth JC, Seargeant LE, Goodman SI. A G-to-T transversion at the +5 position of intron 1 in the glutaryl CoA dehydrogenase gene is associated with the Island Lake variant of glutaric acidemia type I. Hum Mol Genet. 1995; 4:493–495. [PubMed: 7795610]

HaworthJCBoothFAChudleyAEdeGrootGWDillingLAGoodmanSIGreenbergCRMalloryCJMcClartyBMSeshiaSSPhenotypic variability in glutaric aciduria type I: Report of fourteen cases in five Canadian Indian kindreds. J Pediatr and others. 19911185258 [PubMed: 1986098]

Hoffmann GF, Athanassopoulos S, Burlina AB, Duran M, de Klerk JB, Lehnert W, Leonard JV, Monavari AA, Muller E, Muntau AC, Naughten ER, Plecko-Starting B, Superti-Furga A, Zschocke J, Christensen E. Clinical course, early diagnosis, treatment, and prevention of disease in glutaryl-CoA dehydrogenase deficiency. Neuropediatrics. 1996; 27:115–123. [PubMed: 8837070]

Kafil-Hussain NA, Monavari A, Bowell R, Thornton P, Naughten E, O'Keefe M. Ocular findings in glutaric aciduria type 1. J Pediatr Ophthalmol Strabismus. 2000; 37(5):289–93. [PubMed: 11020111]

Knerr I, Zschocke J, Trautmann U, Dorland L, de Koning TJ, Muller P, Christensen E, Trefz FK, Wundisch GF, Rascher W, Hoffmann GF. Glutaric aciduria type III: a distinctive non-disease? J Inherit Metab Dis. 2002; 25:483–490. [PubMed: 12555941]

Koeller DM, Woontner M, Crnic LS, Kleinschmidt-DeMasters B, Stephens J, Hunt EL, Goodman SI. Biochemical, pathologic and behavioral analysis of a mouse model of glutaric acidemia type I. Hum Mol Genet. 2002; 11:347–357. [PubMed: 11854167]

Kolker S, Greenberg CR, Lindner M, Muller E, Naughten ER, Hoffmann GF. Emergency treatment in glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004a; 27:893–902. [PubMed: 15505397]

Kolker S, Koeller DM, Sauer S, Horster F, Schwab MA, Hoffmann GF, Ullrich K, Okun JG. Excitotoxicity and bioenergetics in glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004b; 27:805–812. [PubMed: 15505385]

Kyllerman M, Steen G. Glutaric aciduria. A "common" metabolic disorder? Arch Fr Pediatr. 1980; 37:279. [PubMed: 7406647]

Lindner M, Kolker S, Schulze A, Christensen E, Greenberg CR, Hoffmann GF. Neonatal screening for glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004; 27(6):851–9. [PubMed: 15505392]

Loehr JP, Goodman SI, Frerman FE. Glutaric acidemia type II: heterogeneity of clinical and biochemical phenotypes. Pediatr Res. 1990; 27:311–315. [PubMed: 2320399]

Mandel H, Braun J, el-Peleg O, Christensen E, Berant M. Glutaric aciduria type I. Brain CT features and a diagnostic pitfall. Neuroradiology. 1991; 33:75–78. [PubMed: 2027453]

Morton DH, Bennett MJ, Seargeant LE, Nichter CA, Kelley RI. Glutaric aciduria type I: a common cause of episodic encephalopathy and spastic paralysis in the Amish of Lancaster County, Pennsylvania. Am J Med Genet. 1991; 41:89–95. [PubMed: 1951469]

Muhlhausen C, Ergun S, Strauss KA, Koeller DM, Crnic L, Woontner M, Goodman SI, Ullrich K, Braulke T. Vascular dysfunction as an additional pathomechanism in glutaric aciduria type I. J Inherit Metab Dis. 2004a; 27:829–834. [PubMed: 15505389]

Muhlhausen C, Hoffmann GF, Strauss KA, Kolker S, Okun JG, Greenberg CR, Naughten ER, Ullrich K. Maintenance treatment of glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis. 2004b; 27:885–892. [PubMed: 15505396]

Naughten ER, Mayne PD, Monavari AA, Goodman SI, Sulaiman G, Croke DT. Glutaric aciduria type I: outcome in the Republic of Ireland. J Inherit Metab Dis. 2004; 27:917–920. [PubMed: 15505400]

Neumaier-Probst E, Harting I, Seitz A, Ding C, Kolker S. Neuroradiological findings in glutaric aciduria type I [glutaryl-CoA dehydrogenase deficiency). J Inherit Metab Dis. 2004; 27:869–876. [PubMed: 15505394]

Olsen RK, Andresen BS, Christensen E, Bross P, Skovby F, Gregersen N. Clear relationship between ETF/ETFDH genotype and phenotype in patients with multiple acyl-CoA dehydrogenation deficiency. Hum Mutat. 2003; 22:12–23. [PubMed: 12815589]

Olsen RK, Andresen BS, Christensen E, Mandel H, Skovby F, Nielsen JP, Knudsen I, Vianey-Saban C, Simonsen H, Gregersen N. DNA-based prenatal diagnosis for severe and variant forms of multiple acyl-CoA dehydrogenation deficiency. Prenat Diagn. 2005; 25:60–64. [PubMed: 15662686]

Pineda M, Ribes A, Busquets C, Vilaseca MA, Aracil A, Christensen E. Glutaric aciduria type I with high residual glutaryl-CoA dehydrogenase activity. Dev Med Child Neurol. 1998; 40:840–842. [PubMed: 9881681]

Strauss KA, Morton DH. Type I glutaric aciduria, part 2: a model of acute striatal necrosis. Am J Med Genet C Semin Med Genet. 2003; 121:53–70. [PubMed: 12888986]

Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria, part 1: natural history of 77 patients. Am J Med Genet C Semin Med Genet. 2003; 121:38–52. [PubMed: 12888985]

Tortorelli S, Hahn SH, Cowan TM, Brewster TG, Rinaldo P, Matern D. The urinary excretion of glutarylcarnitine is an informative tool in the biochemical diagnosis of glutaric acidemia type I. Mol Genet Metab. 2005; 84:137–143. [PubMed: 15670719]

Varadkar S, Surtees R. Glutaric aciduria type I and kynurenine pathway metabolites: a modified hypothesis. J Inherit Metab Dis. 2004; 27:835–842. [PubMed: 15505390]

Woelfle J, Kreft B, Emons D, Haverkamp F. Subdural hemorrhage as an initial sign of glutaric aciduria type 1: a diagnostic pitfall. Pediatr Radiol. 1996; 26:779–781. [PubMed: 8929376]

Yager JY, McClarty BM, Seshia SS. CT-scan findings in an infant with glutaric aciduria type I. Dev Med Child Neurol. 1988; 30:808–811. [PubMed: 3069526]

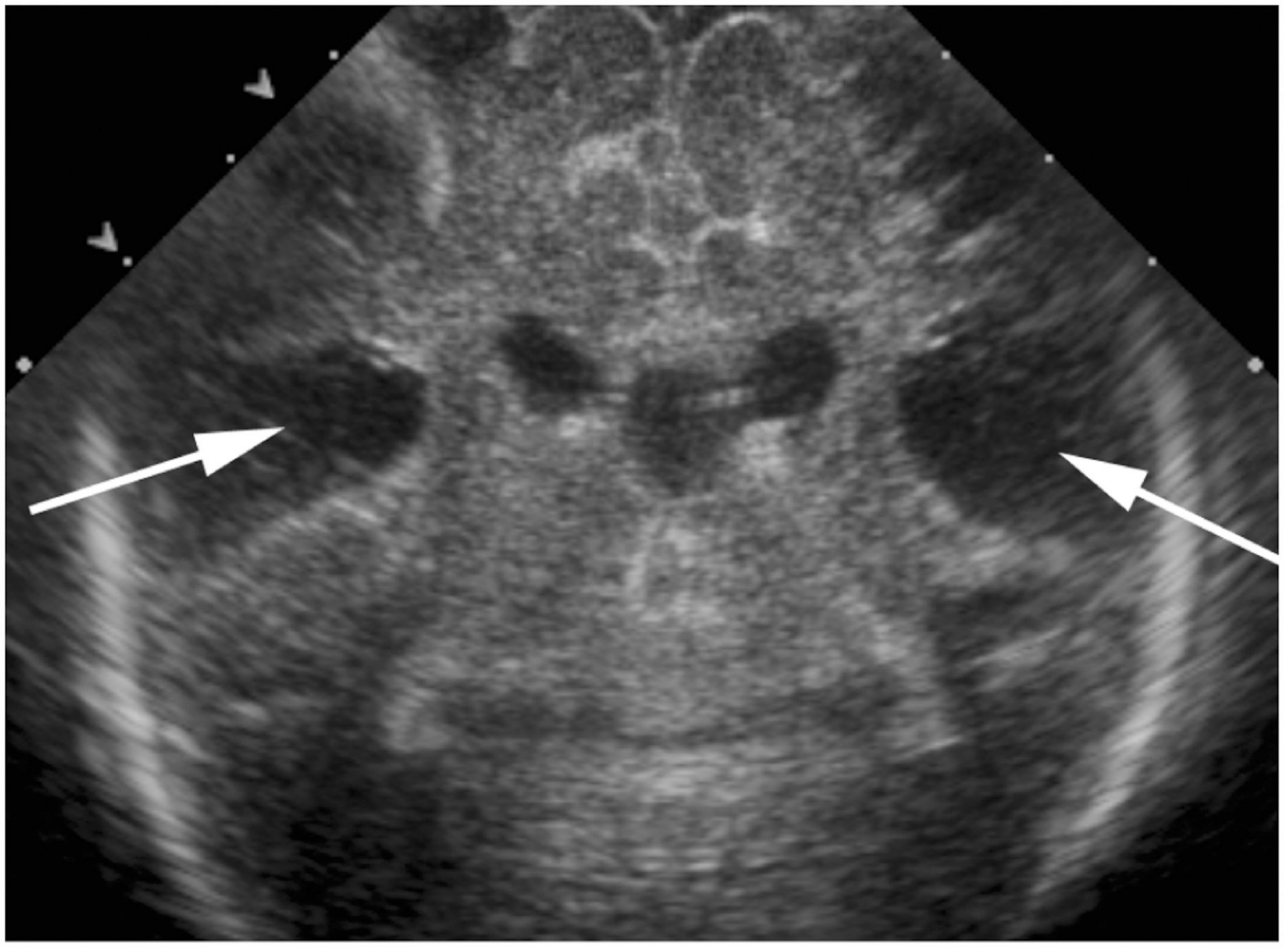

Fig. 1. Head ultrasound in glutaric acidemia type 1

Coronal cerebral sonography through the anterior fontanelle of an infant shows enlargement of the Sylvian fissures (arrows).

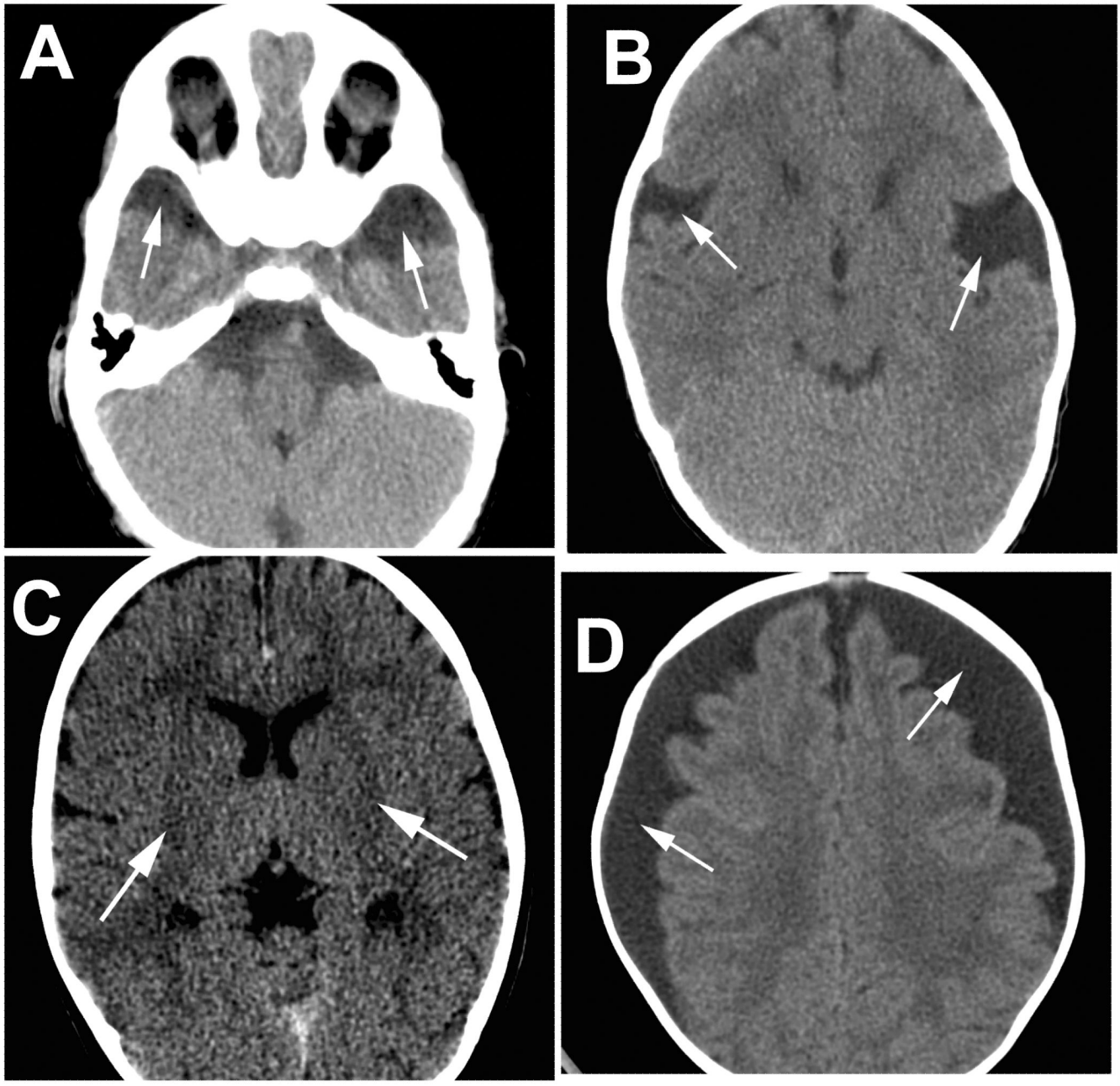

Fig. 2. Non Enhanced axial Computed Tomography (NECT) in glutaric acidemia type 1

A. Expanded anterior middle cranial fossa subarachnoid spaces secondary to frontotemporal atrophy (arrows). B. "Batwing" appearance of the prominent Sylvian fissures (arrows). C. Decrease in attenuation of the putamen bilaterally (arrows). D. Large bilateral convexity subdural hygromas (arrows).

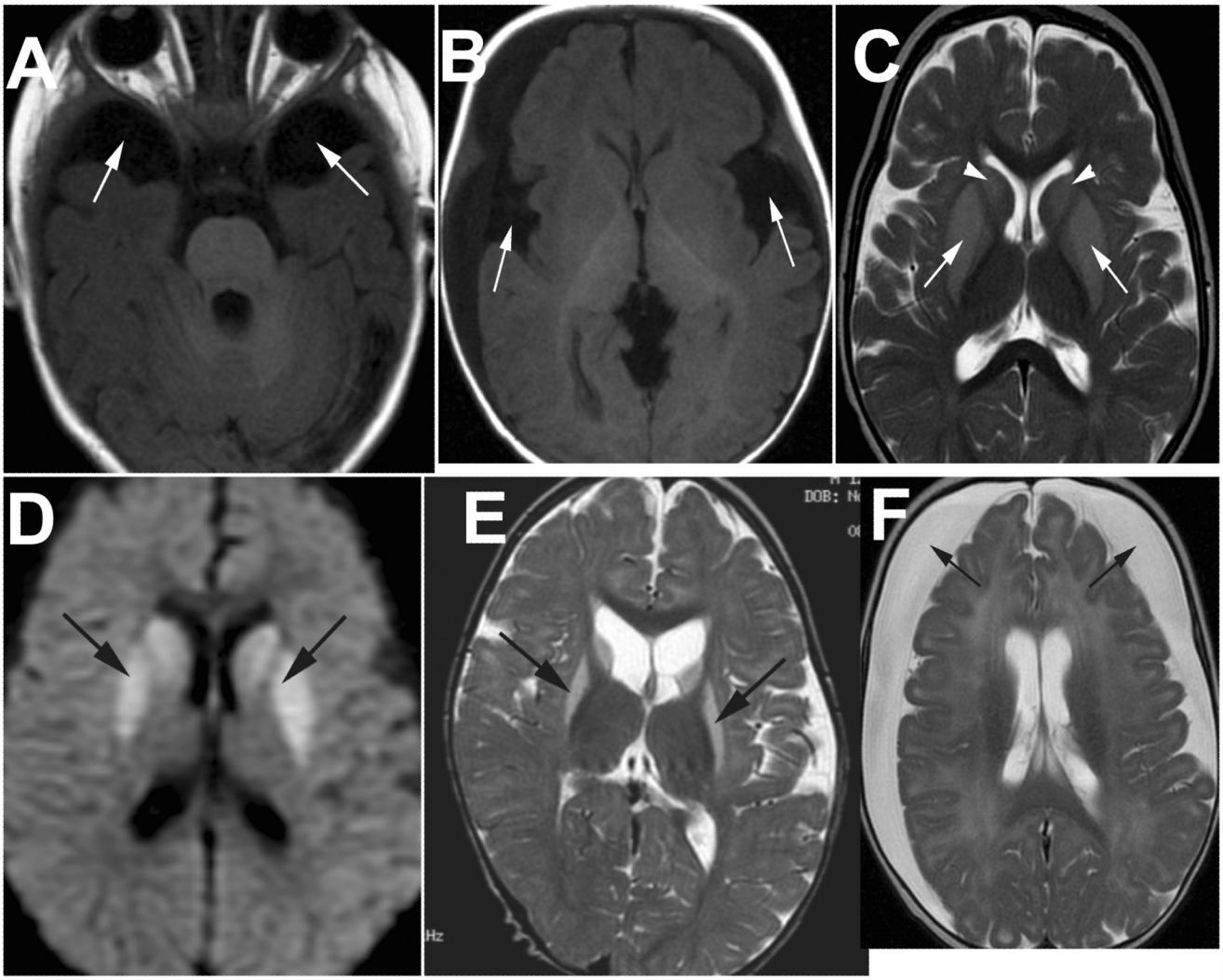

Fig. 3. Brain MRI in patients with glutaric acidemia type 1

A. Axial T1 weighted MR image showing enlarged subarachnoid spaces within the middle cranial fossa anterior to the temporal lobes (arrows). **B**. Axial T1 weighted MR image demonstrating squared or “batwing” appearance of the enlarged Sylvian fissures (arrows). **C**. Axial T2 weighted MR image shows edematous and hyperintense putamen (arrows) and caudate nuclei (arrowheads). **D**. Axial diffusion weighted MR image demonstrates diffusion restriction within the lentiform nuclei (arrows). **E**. Axial T2 weighted MR image shows hyperintense atrophic putamen (arrows). **F**. Axial T2 weighted MR image demonstrates hyperintense large bilateral subdural hygromas (arrows).

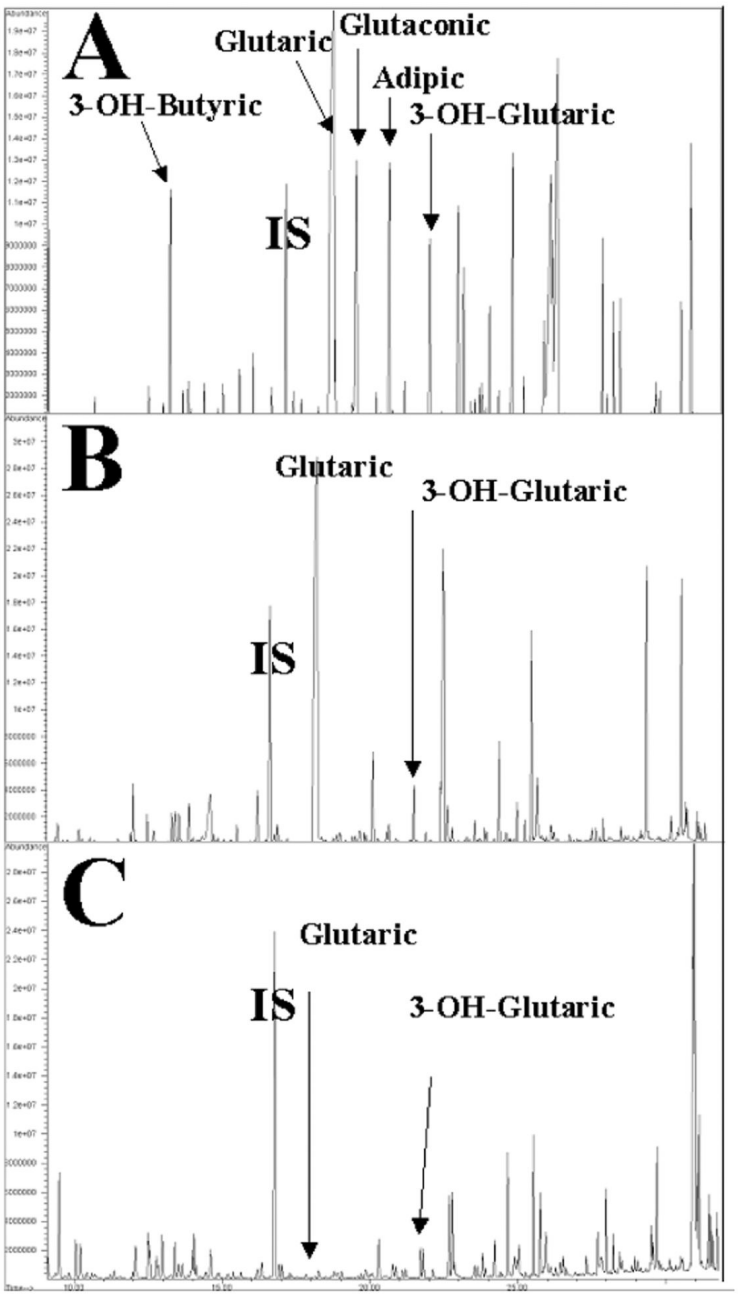

Fig. 4. Urine organic acids in glutaric acidemia type 1

A. Initial presentation with increase in glutaric (>3,500 mmol/mol creatinine), 3-OH-glutaric acid (1,070 mmol/mol creatinine), glutaconic acid and ketone bodies. **B**. Glutaric acidemia type I in good metabolic control. Glutaric (2,587 mmol/mol creatinine) and 3-OH-glutaric acid (219 mmol/mol creatinine) were elevated. **C**. Isolated increase in 3-OH-glutaric acid (69 mmol/mol creatinine), with normal glutaric acid (7 mmol/mol creatinine) at presentation in a patient with glutaric acidemia type I. IS=internal standard.

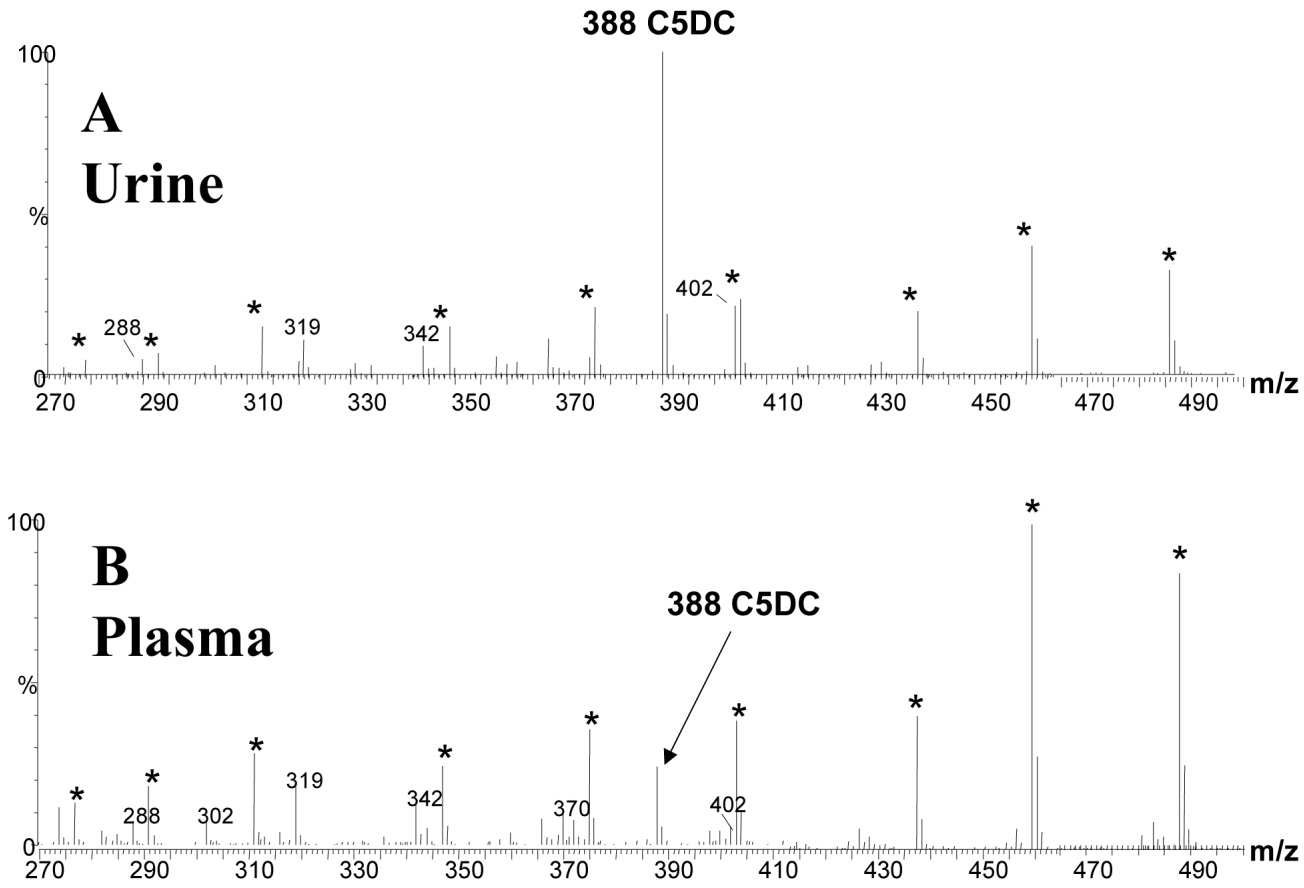

Fig. 5. Urine (A) and plasma (B) acylcarnitine profile in glutaric acidemia type 1

C5-DC (Glutaryl) carnitine is increase above normal in plasma and is usually the highest peak in the urine acylcarnitine profile. Low excretors can have normal plasma acylcarnitine profile. *=Deuterated standards.

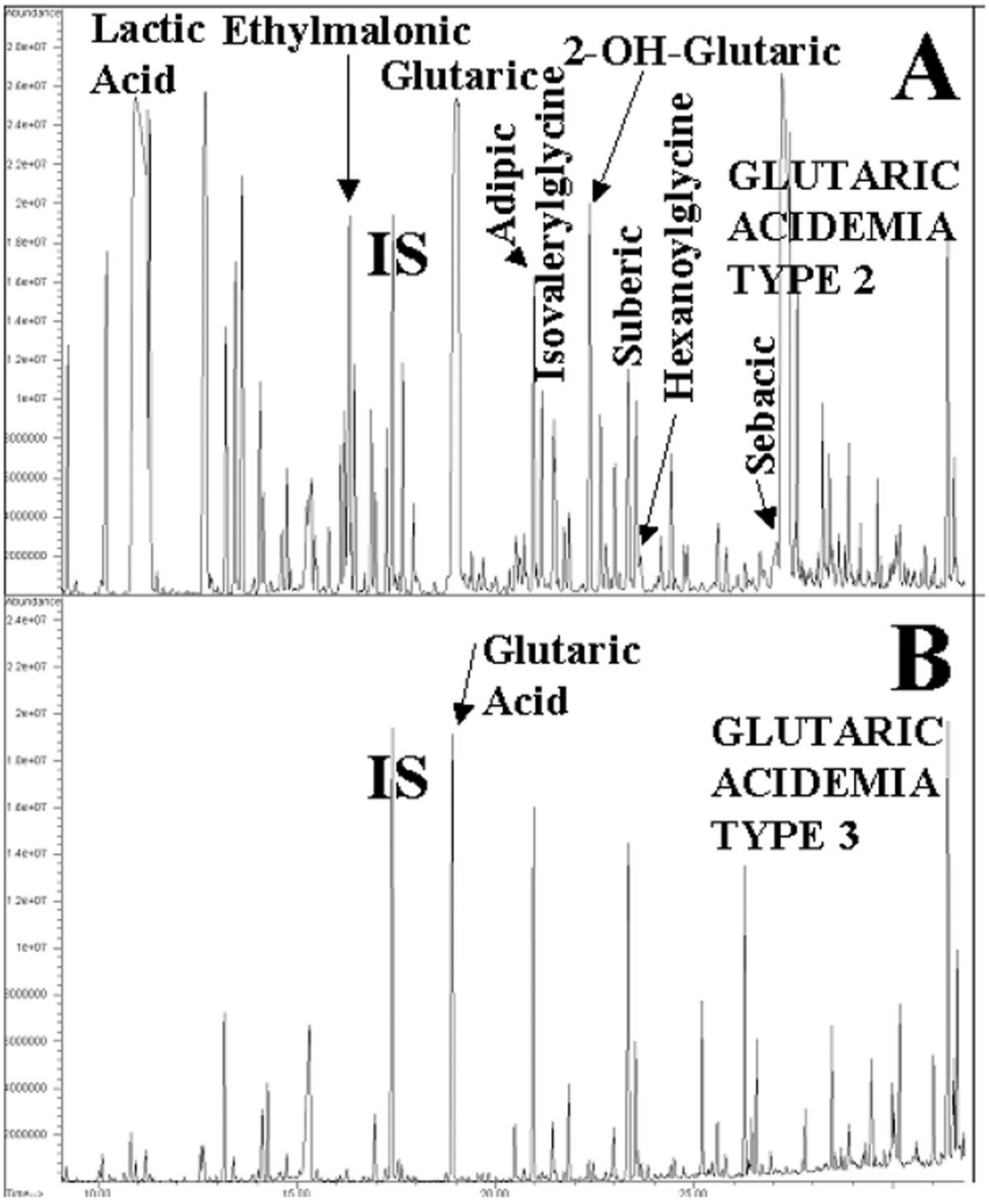

Fig. 6. Urine organic acids in glutaric acidemia type 2 (A) and 3 (B)

A. In glutaric acidemia type 2, in addition to glutaric acid, other metabolites elevated are: isovaleric, lactic and pyruvic, ethylmalonic, 2-OH-glutaric, dicarboxylic acids, reflecting impairment of multiple dehydrogenases. **B**. In glutaric acidemia type 3, there is an isolated increase in glutaric acid. IS=internal standard.