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By : Ghoul Nassema

Amroune Hafida

Loukriz Naouel

TOPIC

Glutaric aciduria type 1 disease

Jury :

Dr. Harrar Nacer	Mohamed Boudiaf M'sila University	Chairman
Dr. Ben cheikh Dalila	Mohamed Boudiaf M'sila University	Supervisor
Dr. Drif Seifeddine	Mohamed Boudiaf M'sila University	Examiner

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DEDICATION

I dedicate this thesis with immense gratitude and love to my incredible family, who have been my unwavering support system throughout my academic journey. Your boundless love and encouragement have been the driving force behind my achievements, and I would not have reached this milestone without you by my side. Thank you for your sacrifices and for believing in me even when I doubted myself.

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In conclusion, I hope that this humble work serves as a meaningful contribution to the field, and I look forward to sharing it with the academic community."

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Contents

abstract

Glutaric acidemias are a group of illnesses that cause an elevated excretion of glutaric acid in the urine. A glutaryl-CoA dehydrogenase deficit leads to lysine, hydroxylysine, and tryptophan metabolism disorders, including glutaric acidemia type 1 (GA-1). Glutaric acid and 3-hydroxyglutaric acid build up as a result. Patients who are affected may exhibit acute dystonia due to striatal degeneration, brain shrinkage, and macrocephaly. Usually, a pediatric illness that is concurrently causing fever between the ages of 6 and 18 months is the cause of these symptoms. Elevated glutaryl (C5DC) carnitine can be utilized to detect this problem during neonatal screening. Urine's acylcarnitine profile typically peaks at glutaryl carnitine, whereas an excess of 3-OH-glutaric acid is found in the urine's organic acid analysis.

The pre-symptomatic start of metabolic treatment, which includes a low-lysine diet, carnitine supplementation, and more intensive emergency care during catabolic episodes, is contingent upon newborn screening. These interventions together have significantly improved neurological outcomes. On the other hand, motor dysfunction already present due to striatal injury can’t be corrected by starting treatment after symptoms appear. Following the onset of striatal damage vulnerability, which occurs at age 6, dietary treatment can be loosened. It is still unknown, though, how dietary relaxation would affect long-term results.

Keywords: glutaric acidemia, macrocephaly, glutaryl-CoA dehydrogenase, dystonia, (C5DC), Newborn screening , carnitine, striatal damage.

ملخص

إن حمض الغلوتاريك الحامضي الجلوتاريك هو مجموعة من الأمراض التي تسبب ارتفاع إفراز حمض الغلوتاريك في البول. يؤدي العجز في نازعة هيدروجين الغلوتاريل-كوا إلى اضطرابات استقلاب اللايسين والهيدروكسي ليسين والتريبتوفان، بما في ذلك حمض الغلوتاريك الحامضي من النوع 1 (GA-1). ويتراكم حمض الجلوتاريك وحمض 3-هيدروكسي الجلوتاريك نتيجة لذلك. قد يعاني المرضى المصابون من خلل التوتر العضلي الحاد بسبب التنكس المخطط وانكماش الدماغ وتقلص الدماغ وصغر الرأس. وعادةً ما يكون سبب هذه الأعراض هو مرض الأطفال الذي يسبب الحمى في الوقت نفسه بين عمر 6 أشهر و18شهراً . يمكن الاستفادة من ارتفاع نسبة الغلوتريل (C5DC) كارنيتين للكشف عن هذه المشكلة أثناء فحص حديثي الولادة. وعادةً ما يصل مستوى الأسيل كارنيتين في البول إلى ذروته في تحليل حمض الغلوتاريل كارنيتين، في حين أن زيادة حمض 3-أوه-جلوتاريك في تحليل الأحماض العضوية في البول.

ويتوقف بدء العلاج الاستقلابي قبل ظهور الأعراض، والذي يتضمن نظامًا غذائيًا منخفض الليزين، ومكملات الكارنيتين، ورعاية طارئة أكثر كثافة أثناء نوبات التقويض، على فحص حديثي الولادة. وقد أدت هذه التدخلات معاً إلى تحسين النتائج العصبية بشكل كبير. من ناحية أخرى، لا يمكن تصحيح الخلل الوظيفي الحركي الموجود بالفعل بسبب إصابة المخطط من خلال بدء العلاج بعد ظهور الأعراض. بعد ظهور الضعف الحركي للمخطط، والذي يحدث في سن السادسة، يمكن تخفيف العلاج الغذائي بعد ظهور ضعف الضرر المخططي، والذي يحدث في سن السادسة. ومع ذلك، لا يزال من غير المعروف كيف سيؤثر التخفيف الغذائي على النتائج على المدى الطويل.

الكلمات المفتاحية: حمض الغلوتاريك الحامضي، صغر الرأس، نازعة هيدروجين الغلوتريل-كوا ديهيدروجينيز، خلل التوتر، (C5DC)، فحص حديثي الولادة، الكارنيتين، تلف المخطط.

Résumé

Les acidémies glutariques sont un groupe de maladies qui provoquent une excrétion élevée d'acide glutarique dans l'urine. Un déficit en glutaryl-CoA déshydrogénase entraîne des troubles du métabolisme de la lysine, de l'hydroxylysine et du tryptophane, y compris la glutaric acidémie de type 1 (GA-1). L'acide glutarique et l'acide 3-hydroxy s'accumulent en conséquence. Les patients atteints peuvent présenter une dystonie aiguë due à une dégénérescence striatale, un rétrécissement du cerveau et une macrocéphalie. En règle générale, ces symptômes sont causés par une maladie pédiatrique qui entraîne simultanément de la fièvre entre 6 et 18 mois. On peut utiliser un niveau élevé de glutaryl (C5DC) carnitine afin de repérer ce problème lors du dépistage néonatal. En général, la glutaryl carnitine est le niveau le plus élevé de l'acyl carnitine dans l'urine, tandis qu'un excès d'acide 3-OH-glutarique est observé dans l'analyse de l'acide organique in urinaire.

Le début pré-symptomatique du traitement métabolique, qui comprend un régime pauvre en lysine, une supplémentation en carnitine et des soins d'urgence plus intensifs pendant les épisodes cataboliques, dépend du dépistage néonatal. Ces interventions combinées ont considérablement amélioré les résultats neurologiques. D'autre part, le dysfonctionnement moteur déjà présent en raison d'une lésion striatale ne peut pas être corrigé en commençant le traitement après l'apparition des symptômes. Après l'apparition de la vulnérabilité aux lésions striatales, qui survient à l'âge de 6 ans, le traitement diététique peut être assoupli. On ignore encore, cependant, comment la relaxation alimentaire affecterait les résultats à long terme."

Mots-clés: acidémie glutarique, macrocéphalie, glutaryl-CoA dehydrogenase, dystonie, (C5DC), dépistage néonatal, carnitine, atteinte striatale.

List of abbreviations

3-OH-GA: 3-Hydroxyglutaric acid

AA: Amino acids

AAM: Amino acid mixture

BT-A: Botulinum toxin type A

C5DC: Glutaryl carnitine

CNS : Central Nervous System

DBS: Dried blood spots

EFSA: European Food Safety Authority

FAD: flavin adenine dinucleotide

GA: Glutaric acid

GA-I: Glutaric aciduria type I

GCDH: Glutaryl-CoA dehydrogenase

GC-MS: gas chromatography–mass spectrometry

IV: Intra Veineux

MHM: Metabolic Hereditary Disease

MRI: Magnetic Resonance Imaging

MS/MS: tandem mass spectrometry

NBS: newborn screening

NE : Enteral nutrition

RNA: Ribonucleic acid

RNP: Nutritional references for the population

TE: total energy intake

VMO: Vitamins Minerals Trace elements

List of figures

List of tables

Introduction

Introduction

Inherited disorders of metabolism (IDM), also known as inborn errors of metabolism, are rare but often serious diseases (with a prevalence ranging from 1 in 5,000 to 1 in 500,000 births). They are linked to mutations in genes encoding enzymatic proteins, channel proteins, transporter proteins, receptors, or proteins involved in intra/intercellular signal transmission. Presently, around 500 diseases have been identified, but this number could be as high as 4,000 to 6,000 if all genes encoding these proteins are considered (Sedel, 2012).

In addition, hereditary metabolic diseases fall into four main categories: intoxication diseases linked to an accumulation of toxic metabolites (e.g., urea cycle deficiencies), energy metabolism diseases (e.g., fatty acid oxidation deficiencies), vitamin-dependent diseases, and anomalies in the synthesis or catabolism of complex molecules (Brassier, 2015).

Glutaryl-CoA dehydrogenase (GCDH, EC 1.3.99.7) deficiency, also known as glutaric acidemia or aciduria type I, which is considered as one of the major toxic metabolic,is an autosomal recessive disease first described in 1975 (Goodman *et al*., 1975). It has an estimated overall prevalence of 1 in 100,000 newborns (Lindner *et al*., 2004).

Since the description of the first two patients in 1975 (Goodman *et al*., 1975), more than 400 patients have been identified worldwide. Three genetic isolates with a high carrier frequency (up to 1:10) and over-representation of this disease have been identified, including the Amish Community (Morton *et al.,* 1991), Canadian Oji-Cree Indians (Haworth *et al*., 1991), and the Irish Travellers (Naughten *et al*., 2004).

The main objective of this study is to establish the current state of knowledge and practices among pharmacists, pharmacy interns, and pediatric interns regarding hereditary metabolic diseases at risk of decompensation. Specifically, we chose to research glutaric aciduria type 1 disease (GCDH deficiency).

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

Significant differences exist in the diagnostic procedures and management of affected patients, There is considerable variability in outcomes, especially among patients identified before symptoms manifest (Kölker *et al*., 2006).

With the swift growth of neonatal screening for GCDH deficiency, the main objective of this guideline is to review standard practices and create recommendations for diagnosis and treatment based on the most reliable evidenceand management based on the best available evidence.

Untreated, most patients will develop neurological disease during a finite period of brain development (age 3–36 months) following an encephalitis-like, acute encephalopathic crisis often precipitated by febrile illness, immunization, or surgical intervention (Hoffmann *et al*., 1991; Kölker *et al*., 2006). The characteristic neurological sequel of these crises is acute bilateral striatal injury and, subsequently, a movement disorder. Dystonia is the dominant extrapyramidal symptom, often accompanied by spasticity (Hoffmann *et al*., 1991; Kyllerman *et al*., 1994). Morbidity and mortality are high in patients who have experienced a crisis (Kölker *et al*., 2006; Kyllerman *et al*., 2004).

During the last three decades, Efforts have been undertaken to develop and improve therapy for GCDH deficiency. Dietary management, along with oral supplementation of L-carnitine and occasionally riboflavin during maintenance treatment, and enhanced emergency treatment during episodes of intercurrent illness, are employed for most patients. This therapeutic approach has significantly decreased the occurrence of acute encephalopathic crises, thereby lowering morbidity and mortality in those diagnosed early. patients (Kölker *et al*., 2006; Monavari and Naughten, 2000; Strauss *et al*., 2003).

In this study, we will investigate the origin of the disease, the age groups susceptible to it, the initial symptoms observed in patients, the diagnosis made by specialists, and the treatment plan based on metabolic symptoms and age group.

Chapter I:

Glutaryl coenzyme dehydrogenase

I. Glutaryl coenzyme A dehydrogenate (GCDH)

I.1. Definition Glutaryl-CoA dehydrogenate

GCDH) is an enzyme encoded by the GCDH gene located on chromosome19. It belongs to family (class1) the acyl-CoA dehydrogenase (Lindner *et al*., 2004).

The GCDH gene, is situated on chromosome 19p13.13 consists of 12 exons, giving rise to two alternatively spliced mRNAs. These RNAs encode proteins of 438 amino acids (isoform a) and 428 amino acids (isoform b). The isoform b protein is not functional as a glutaryl-CoA dehydrogenase. the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA and carbon dioxide, playing a crucial role in the degradative pathway of L-lysine, L-hydroxylysine, and L-tryptophan metabolism (Lindner *et al*., 2004).

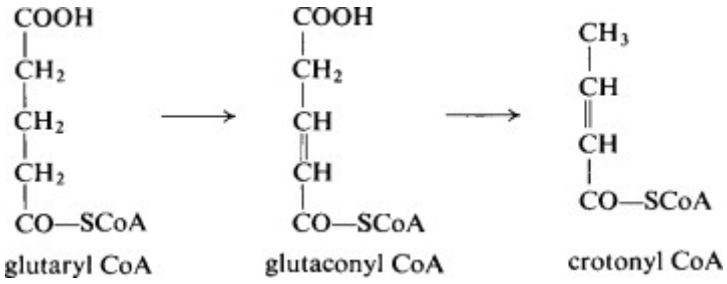

Figure 1: Rol of glutaryl COA dehydrogenas (Koeller *et al*., 2002).

I.2. Structure:

The structure of glutaryl-CoA dehydrogenase comprises a large alpha-helical domain that houses the enzyme's active site, which is essential for its dehydrogenase activity. Within this domain, the cofactor FAD (flavin adenine dinucleotide) plays a crucial role. Additionally, the enzyme features a small beta-sheet domain, which aids in stabilizing the overall protein structure. This domain is vital for maintaining the correct orientation of active site residues and facilitating substrate binding and catalysis (Rao *et al*., 2006).

Molecular Formula of glutryle CoA dehydrogenaseis: $C_9H_{13}N_3O_9P_1S_1$, The molecular formula of an enzyme provides information about the number of atoms of each element present in the enzyme's structure. In the case of glutaryl dehydrogenase, the molecular formula indicates that the enzyme contains 9 carbon atoms, 13 hydrogen atoms, 3 nitrogen atoms, 9 oxygen atoms, 1 phosphorus atom, and 1 sulfur atom (Goodman *et al*., 1975).

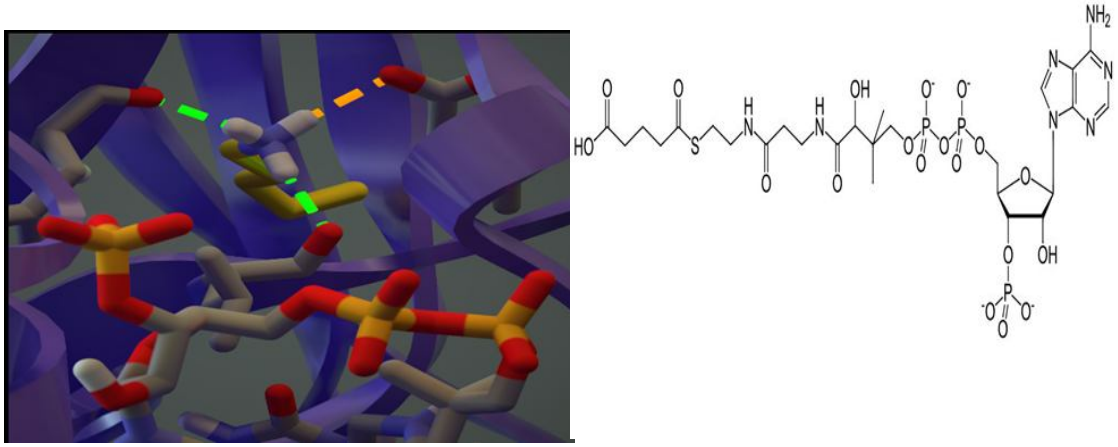

Figure 2: Structure of the glutaryl-coenzyme A dehydrogenase (Rao *et al*., 2006**).**

I.3. Mutation of glutaryl-coenzyme A dehydrogenase

The exact location of a mutation in the GCDH gene can vary among patients with GA-I. However, a common mutation that has been identified in many affected individuals is a substitution of a cytosine for a thymine at position 299 in the coding region of the gene. This mutation results in a single amino acid change from arginine to tryptophan at position 100 in the GCDH protein (Goodman *et al*., 1998).

In addition to the mutation at position 299, several other mutations have been identified in the GCDH gene that are associated with GA-I. These mutations can occur throughout the gene and can result in a variety of changes to the GCDH protein, including deletions, insertions, and missense mutations (Sampath *et al*., 2015).

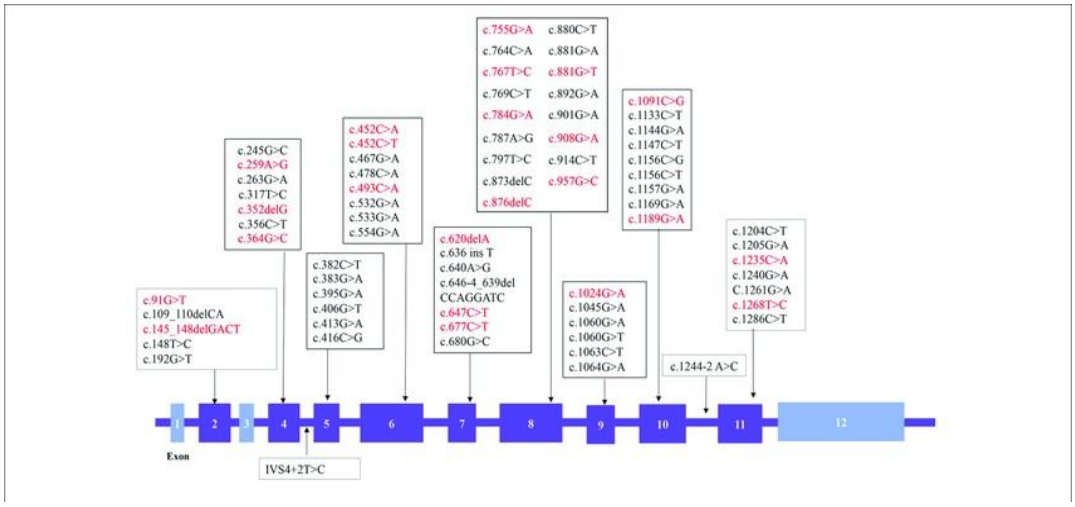

Figure 3: Mutation of glutaryl-coenzyme A dehydrogenase (Gurbuz *et al*., 2020).

I.4. The Role of Lysine and Tryptophan in the Body

I.4.1. Lysine and Tryptophan as Amino Acids

Lysine and tryptophan are two essential amino acids vital for various metabolic processes in the body. Lysine participates in the synthesis of proteins, collagen, carnitine, and certain neurotransmitters. On the other hand, tryptophan serves as a precursor for the synthesis of serotonin and melatonin (Seibert *et al*., 2020).

Carnitine, a compound synthesized from lysine and methionine, plays a critical role in energy metabolism by facilitating the transportation of fatty acids into the mitochondria for energy production. It can be endogenously synthesized or obtained from dietary sources such as red meat and dairy products. Supplementation with carnitine has been suggested to offer therapeutic benefits in various conditions (Gopinathan *et al.,* 2020; Bremer, 1983).

I.4.2. Pathway of degradation of lysine, hydroxylysine, and tryptophan

The degradation pathways of lysine, hydroxylysine, and tryptophan initially proceed through separate routes, ultimately converging into a common pathway at the point of 2-oxoadipic acid within the mitochondria. This intermediate is then converted to glutaryl-coenzyme A (Glu-CoA) by the 2-oxoglutarate (α-ketoglutarate) dehydrogenase complex. Subsequently, it undergoes oxidative decarboxylation to form crotonyl coenzyme A, catalyzed by the mitochondrial matrix protein glutaryl-CoA dehydrogenase (GCDH). The enzymatically active GCDH is structured as a homo tetramer, containing four flavin adenine dinucleotide (FAD) groups (Goodman *et al.,* 1995).

In addition to homo tetra merization, GCDH interacts with various other mitochondrial proteins, forming multimeric dehydrogenase complexes essential for the efficient metabolism of glutaryl-CoA (Schmiesing *et al*., 2014).

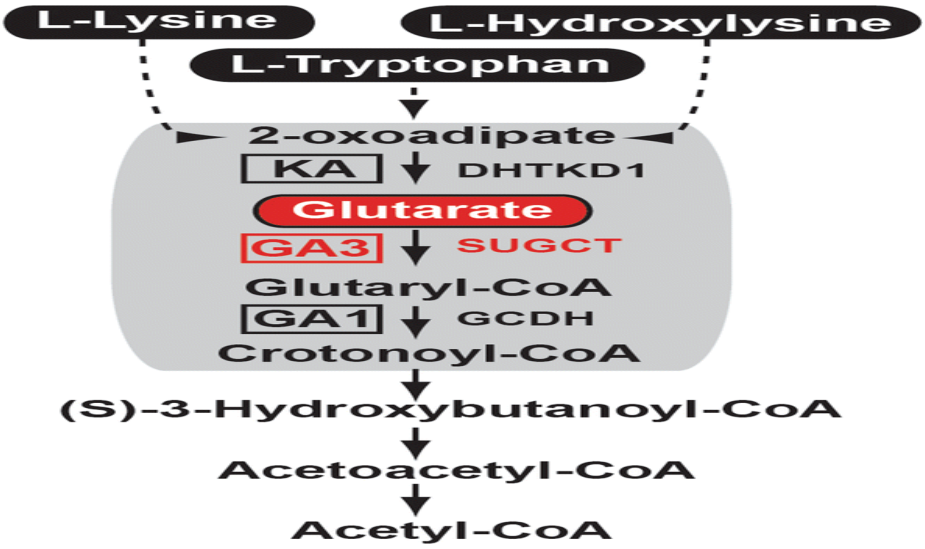

Figure 4: Phathway of degradation of lysine, hydroxylysine and tryptophane **(**Lakshmi *et al.,* 2020).

I.5. Rol of Glutaryl-CoA in the Pathway of Degradation of Lysine and Tryptophan

Glutaryl-CoA metabolism encompasses a series of biochemical reactions responsible for converting glutaryl-CoA into other compounds within the body. Glutaryl-CoA serves as a crucial intermediate in the degradation pathways of lysine and tryptophan, two essential amino acids (João *et al.,* 2020).The process of glutaryl-CoA metabolism involves several enzymes, among which glutaryl-CoA dehydrogenase catalyzes the conversion of glutaryl-CoA to crotonyl-CoA. Crotonyl-CoA is subsequently metabolized within the mitochondria to produce acetyl-CoA, a molecule that can enter the citric acid cycle (Krebs) for energy production (Koeller *et al.,* 2002).

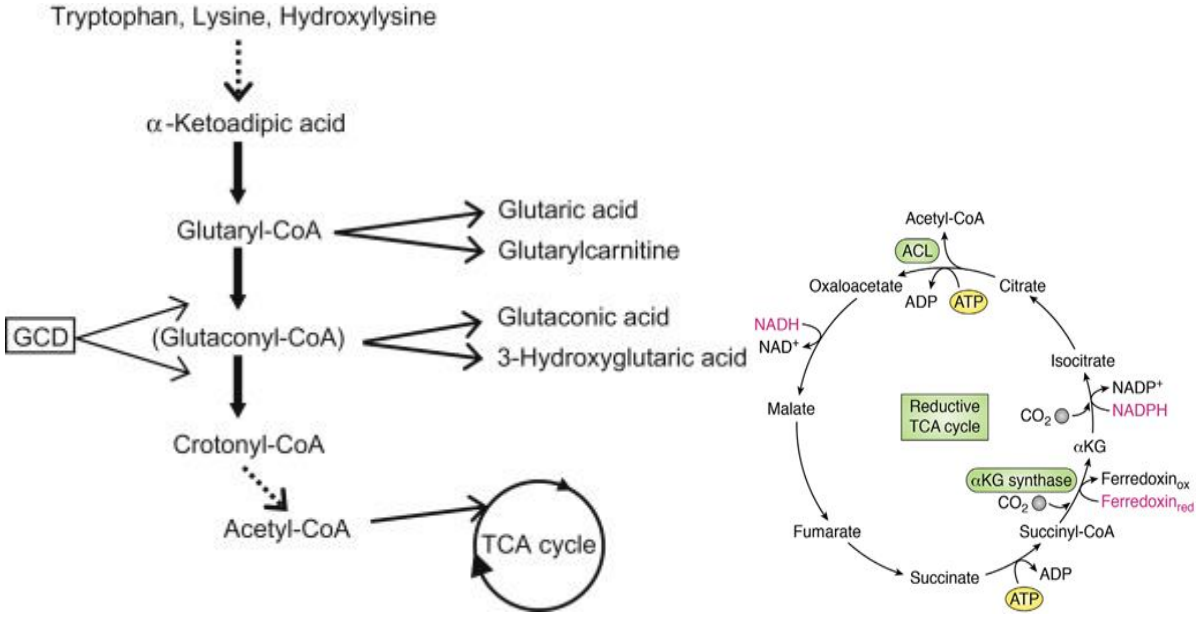

Figure 5: role of glutryle–CoA the pathway of degradation of lysine, tryptophane (Koeller *et al.,* 2002).

Schematic representation of glutaryl-CoA role of glutaryl-CoA I the pathway of degradation of lys, trp metabolism and the role of SUGCT. The interactions between lysine metabolism and the TCA cycle are displayed. The abbreviations are: IDH, isocitrate dehydrogenase; OADHc, 2-oxoadipate dehydrogenase complex; OGDHc, 2-oxoglutarate dehydrogenase complex; SCS, succinyl-CoA synthetase; SUGCT, succinyl-CoA: glutarate-CoAtransferase; TCA, tricarboxylic acid (JoãoL et al., 2020).

I.6. Metabolism of Glutaryl-CoA

Glutaryl-CoA dehydrogenase (GCDH) catalyzes the oxidative decarboxylation of glutaryl-CoA, an intermediate involved in the catabolism of tryptophan, lysine, and hydroxylysine. The deficiency in GCDH activity observed in patients with glutaric acidemia type I (GA-I) results in the accumulation of glutaric acid (GA) and 3-hydroxyglutaric acid (3-OHGA) in the bloodstream (Koeller *et al*., 2002).

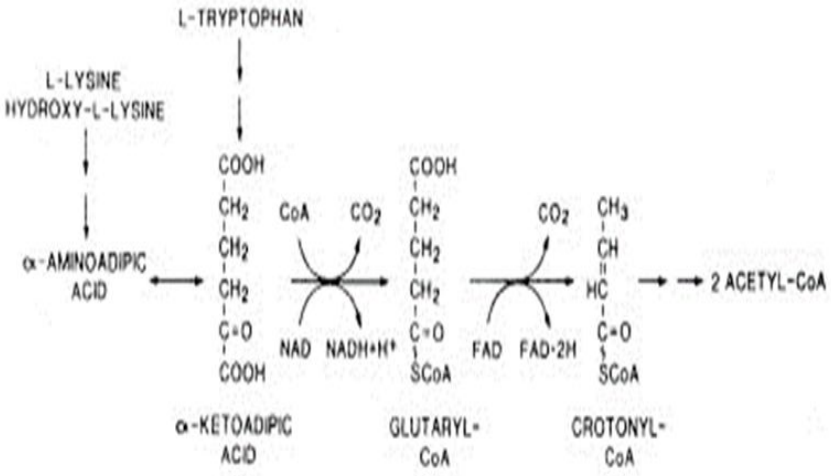

Figure 6 : métabolisme of glutryle coA (Gomes *et al .,* 1981).

GCDH deficiency results in proximal accumulation of glutaryl-coenzyme A (CoA) and its dicarboxylic acid derivatives, glutaric acid (GA) and 3-hydroxyglutaric acid (3HGA). These metabolites become concentrated in the brain due to its limited capacity to form 5-carbon carnitine and glycine conjugates from glutaryl-CoA or export medium-chain dicarboxylates.

Chapter II:

Glutaric aciduria type I disease

Chapter II. Glutaric aciduria Type I disease

II.1. Definition

Genetic mutations impacting glutaryl-CoA dehydrogenase can lead to a deficiency in this enzyme, resulting in metabolic disorders termed glutaryl-CoA dehydrogenase deficiency. This condition can cause the accumulation of glutarate and its derivatives in the body, potentially resulting in adverse health effects, particularly affecting the nervous system (Goodman *et al.,* 1995).

Glutaric aciduria type I manifests due to the inability to metabolize the amino acids lysine, hydroxylysine, and tryptophan. This failure leads to the accumulation of toxic levels of glutaric acid in the body, resulting in damage to the basal ganglia in the brain (Goodman *et al*., 1995).

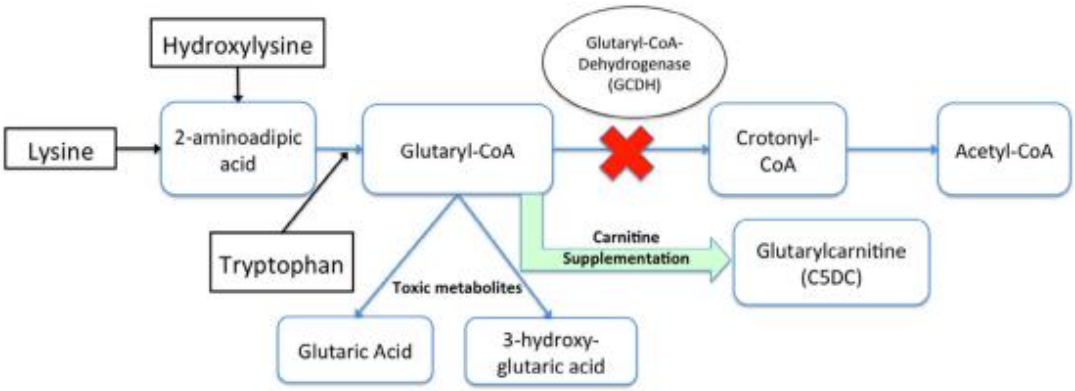

Figure 7: Lysine/ hydroxylysine / tryptophan metabolic pathway (Sauer *et al*., 2011).

II.2. Pathophysiology

Glutaric aciduria type I (GA-1) is an organic aciduria stemming from dysfunction or absence of glutaryl-CoA dehydrogenase, a critical enzyme in the metabolism pathway of lysine, hydroxylysine, and tryptophan. This disruption leads to the inability to produce Acetyl-CoA, a key metabolite crucial for participation in the Krebs cycle (Sauer *et al*., 2011).Similar to other organic acidurias and amino acido pathies, the underlying pathophysiology involves intoxication with by-products, particularly glutaric acid and 3-hydroxyglutaric acid (Singer *et al*., 2016). These by-products lead to enzyme inhibition, substrate deficiencies, and energy deficiency. Due to limited blood-brain barrier permeability, these compounds accumulate in urine and blood, resulting in more pronounced neurotoxic effects, classifying GA-1 as a cerebral organic aciduria. Additionally, there is secondary carnitine depletion. Supplementation with carnitine may prove beneficial in metabolizing glutaryl-CoA to C5DC, thus increasing available Coenzyme A (Sauer *et al*., 2011).

II.3.1. Neurometabolic Disorder of Intoxication of The Brain

The pathomechanisms of brain damage in glutaric aciduria type 1 are not fully understood, but are believed to involve a combination of excitotoxicity, oxidative stress, inflammation, and mitochondrial dysfunction (Wajner., 2021).

Infants with glutaric aciduria type 1 (GA1) are prone to intracranial vascular dysfunction, with the disease-specific metabolite 3-hydroxyglutaric acid (3-OH-GA) inhibiting basal and vascular endothelial growth factor (VEGF)-induced endothelial cell migration. 3-OH-GA affects the morphology of VEGF-induced endothelial tubes due to partial disintegration of endothelial cells (Mühlhausen *et al*., 2006).

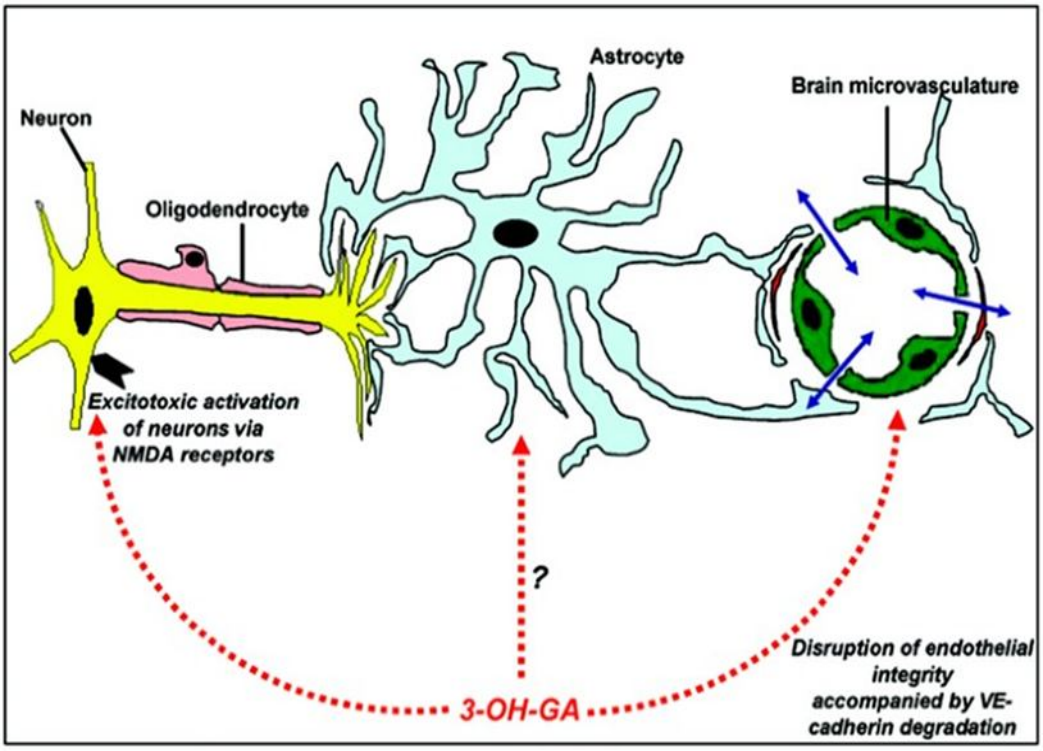

Figure 8: Endothelial effects of 3-hydroxyglutaric acid (Mühlhausen *et al*., 2006).

- **Excitotoxicity:** Glutaric acid and 3-hydroxyglutaric acid have been shown to exert neurotoxic effects, particularly on the striatum, a region of the brain involved in motor control. These metabolites disrupt the balance of excitatory and inhibitory neurotransmitters, leading to excessive neuronal stimulation and subsequent cell death (Liang *et al*., 2021).

- **Oxidative Stress:** The accumulation of glutaric acid and other metabolites increases the production of reactive oxygen species, damaging cell membranes, proteins, and DNA. This oxidative stress contributes to neuronal dysfunction and death (Borsani *et al*., 2001).

- Inflammation: Toxic metabolites trigger an inflammatory response in the brain, activating microglial cells and releasing pro-inflammatory cytokines. Chronic inflammation exacerbates neuronal damage and contributes to brain injury progression (Couce *et al.,* 2013).

- Mitochondrial Dysfunction: Glutaric acid and 3-hydroxyglutaric acid interfere with mitochondrial function, disrupting energy production and increasing vulnerability to oxidative stress. Mitochondrial dysfunction exacerbates neuronal damage in glutaric aciduria type 1 (Brivi *et al., 2022).*

II.3.2. Kidneys

Glutaric aciduria type 1 can lead to kidney damage due to the accumulation of toxic metabolites. Inflammation and oxidative stress in the kidneys impair kidney function and may lead to conditions such as chronic kidney disease or kidney failure. Additionally, high levels of glutaric acid and other metabolites can cause the formation of kidney stones, further impairing kidney function (Baric *et al.,* 1999).

II.3.3. Heart

Accumulation of harmful substances can damage the heart, disrupting energy metabolism and impairing mitochondrial function. This leads to decreased cardiac function and potential malfunction (Hassel *et al.,* 2002).

A mutation in glutaryl CoA dehydrogenase can cause a rare condition called dicarboxyl icmyoglobinuria, affecting multiple organs due to the accumulation of breakdown products of proteins and fats. The effects of this mutation vary depending on its severity and the timing of treatment initiation (Wajner., 2022).

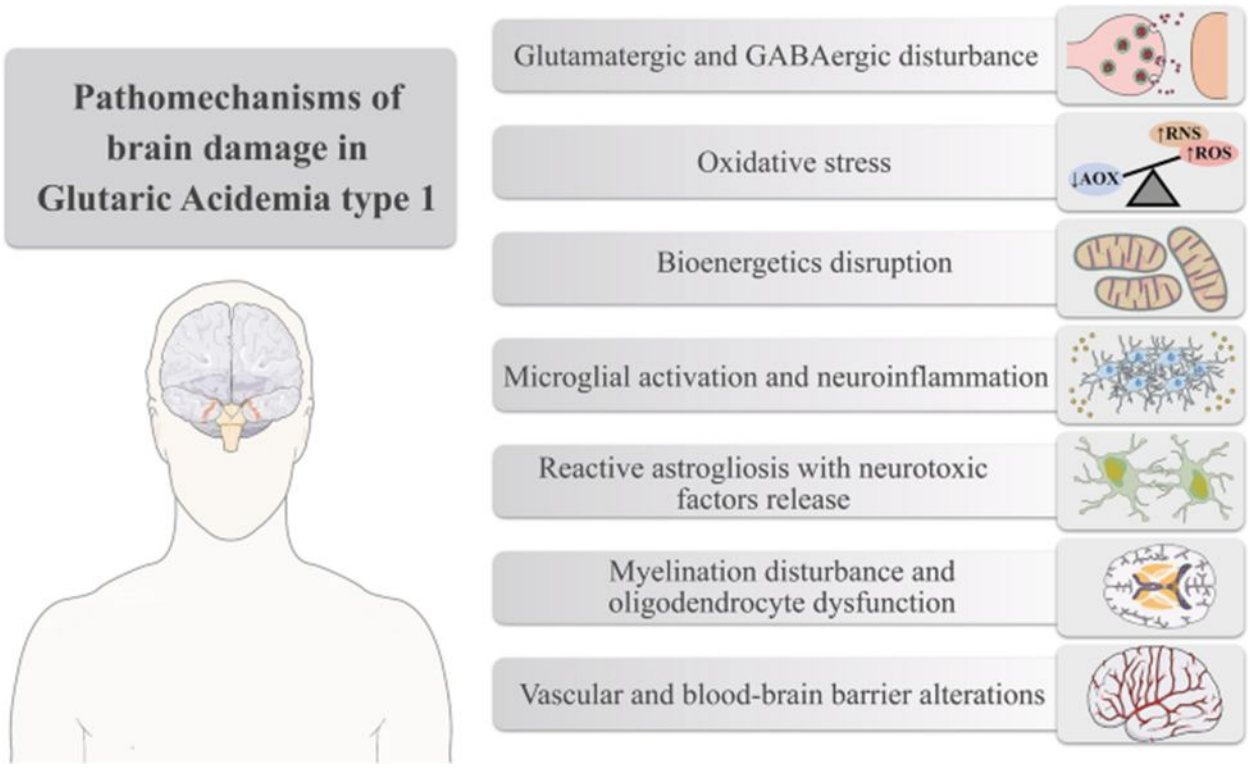

Figure 9: glutaric aciderai type 1 an inheridet neurométaolic disorder of intoxication (Wajner; 2022).

II.4. Deffernce between Glutaric aciduria type 1 and Glutaric aciduria type2

Glutaric aciduria type 1 and glutaric aciduria type 2 are both rare inherited metabolic disorders that affect how the body breaks down specific amino acids. These disorders result in the buildup of toxic substances in the body, leading to a range of symptoms and complications. While both conditions share some similarities, there are key differences between the two that can help in diagnosis and treatment (Goodman *et al*., 1998).

On the other hand, glutaric aciduria type 2 is caused by a deficiency of the enzyme electron transfer flavoprotein or electron transfer flavoprotein-ubiquinone oxidoreductase, which are involved in the metabolism of fatty acids and amino acids. This deficiency results in the buildup of acyl carnitines in the body, leading to similar symptoms as glutaric aciduria type 1. individuals with glutaric aciduria type 2 may also experience liver dysfunction and muscle weakness in addition to neurological symptoms (Strauss *et al.;* 2014).

Chapter III:

Diagnostic and symptoms of Glutaric aciduria type I

Chapter III: Diagnostic and symptoms of Glutaric aciduria type I

III.1. Symptoms

The severity of glutaric acidemia type 1 (GA1) varies widely, ranging from mild to severe manifestations. GA1 can be categorized into two clinical entities: GA-1 diagnosed at birth or pre-birth, managed through dietary restrictions, and GA-1 diagnosed after an encephalopathic crisis. Although a crisis may occur under both scenarios, individuals diagnosed before a crisis can often avoid most or all injury through proper management (Jinfu *et al*., 2023).

III.1.1. Baby Symptoms

Symptoms of GA1 typically emerge several months after birth. However, some babies with GA1 may present with macrocephaly (larger-than-average head) or muscle weakness (hypotonia).
Within the first three years of life, individuals with GA1 may experience an acute encephalopathic crisis, leading to brain damage, movement problems, developmental delays, seizures, and intracranial bleeding. Early clinical signs indicating an acute encephalopathic crisis include:

- Lack of appetite or difficulty feeding
- Fatigue
- Irritability
- Jitteriness
- Muscle weakness
- Nausea, vomiting, and diarrhea (Morales., 2023).

Figure 10 : Baby Symptoms (Zihan *et al*., 2023)

Infant with Classical Glutaric aciduria

(A) Clinical photo displays a large head, protrusion of the tongue due to lingual dystonia, and dystonia of the right upper limb.

(B) MRI of the same child demonstrates bilateral basal ganglionic and periventricular hyperintensities with widening of bilateral sylvian fissures.

(C) MRI of a different child illustrates hyperintensities involving bilateral globuspallidi, periventricular white matter, widening of bilateral sylvian fissures, and subdural collections (Zihan *et al*., 2023).

III.1.2. Symptoms in Adults

In some cases, symptoms of glutaric aciduria may onset during adolescence or adulthood (typically between 15 and 19 years old). These symptoms may include nonspecific neurological manifestations such as headaches, vertigo, and reduced fine motor skills.

Individuals with glutaric aciduria may also experience metabolic crises, which occur when compounds such as organic acids accumulate to dangerously high levels. Stressors such as illness and fasting can trigger these metabolic crises (Balamurugan., 2021).

Figure 11: symptom in adults; Clinical photograph of siblings showing dystonia *(white arrows in A) in the resting state and increased dystonia when extending the limbs (white arrows1B)* (Balamurugan., 2021).

III.2. Diagnostic

Nearly all babies will undergo a simple blood test, known as a heel-prick test,toscreen the conditions such as GA1that may not be immediately apparent. This screening method aids in identify metabolic disorders likeGA1 (Märtner *et al*., 2021).

If the test results are unusual, a metabolic team conducts further testing to confirm the diagnosis. Such a team typically consists of a metabolic doctor, dietitian, and nurse specialist. The diagnostic workup typically includes blood and urine tests to measure the levels of glutaric acid and related compounds.Healthcare professionals may conduct GCDH enzyme analysis or genetic testing for a GCDH gene variant to confirm the diagnostics (Shaik *et al*., 2019).

III.2.1. Diagnostic prenatal

For couples at risk, prenatal diagnosis (PND) or preimplantation diagnosis by genetic study may be considered, provided that the two pathogenic variants in the GCDH gene have first been identified in the index case. PND by molecular study, involving the search for familial mutations in fetal DNA extracted from chorionic villi (from 11 weeks' gestation) or amniotic fluid (from 15 weeks' gestation). Alternatively, if the causal mutations have not been identified, PND can be performed by assaying metabolites (AG and 3-OH-GA and C5DC) in the amniotic fluid supernatant (Foran *et al*., 2021).

However, these assays should be conducted in laboratories with sufficiently sensitive quantification methods and with authorization for PND by biochemical study. In some cases, certain echographic signs and abnormalities detected on fetal MRI, although not very specific, may suggest an AG-I fetus: such as lack of closure of the sylvian valleys, germinolysis cysts, and macrocephaly with widening of the sylvian valleys. In suchcontext, measuring AG and 3-OH-GA C5DC (glutaryl carnitine**)** in the amniotic fluid supernatant is also possible (Larson *et al*., 2019).

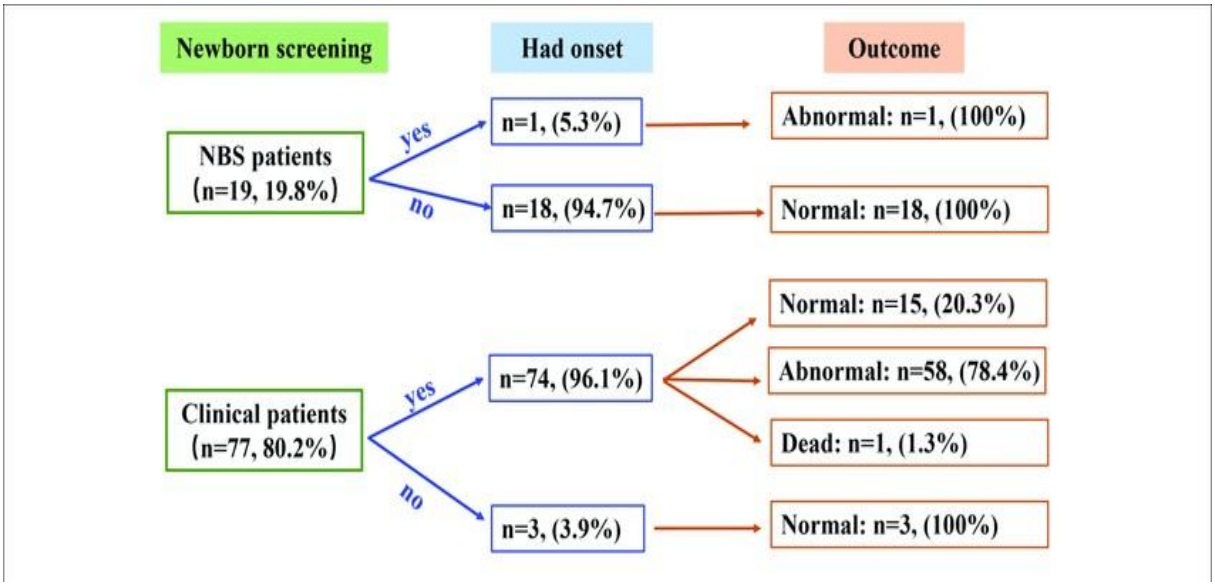

Figure 12: Summary of the newborn screening status, disease onset, and clinical outcome data for the participants in this study (Boy *et al*., 2018).

III.2.2. Genetic testing

Glutaric aciduria type 1 can be diagnosed through genetic tests aimed at detecting mutations in the genes responsible for the condition. GA-I is inherited in an autosomal recessive manner. The risk of recurrence is 1 in 4 with each pregnancy for couples at risk. Genetic counseling must be carried out within the framework of a dedicated consultation (Boy *et al*., 2013).

III.2.3. Magnetic Resonance Imaging (MRI)

MRI can reveal brain abnormalities such as ventricular dilatations and tissue alterations that support the diagnosis. Utilizing MRI brain scans, it has been observed that leuko encephalopathy and aberrant signals from the basal ganglia are among the most common symptoms of this illness, alongside widened Sylvian fissures of the frontotemporal lobes and an arachnoid cyst) (Han *et al*., 2015).

Table 1: Clinical features and MRI findings of patients with Glutaric aciduria type 1 (GA1) (Han *et al*., 2015).

Clinical features (N = 101)	**%**	**MRI flindings (N= 59)**	**%**
Macrocephaly	44.6	**Wide sylvian fissures**	47.5
Movement Disorders	41.6	**Abnormal signal of bilateral basal ganglia**	35.6
Seizure	39.6	**Leukoen cephalopathy**	28.8
Mental retardation	34.7	**Wide ventricle**	27.1
Muscular hypotonia	31.7	**Cerebral atrophy**	23.7
Coma	10.9	**Arachnoid cysts**	20.3
Feeding difficulty	21.8	**Hydrocephalus/subdurale ffusion**	13.6
Vomiting	23.8	**Subdural hematomas**	6.8
Failure to thrive	13.9	**Myelination delay**	3.4
Diarrhea	13.9	**Abnormal brainstem/cerebellum signaling**	3.4
Jaundice	11.9	**brainstem/cerebellum signaling**	1.7
Abnormal Respiration	6.9	**Normal**	

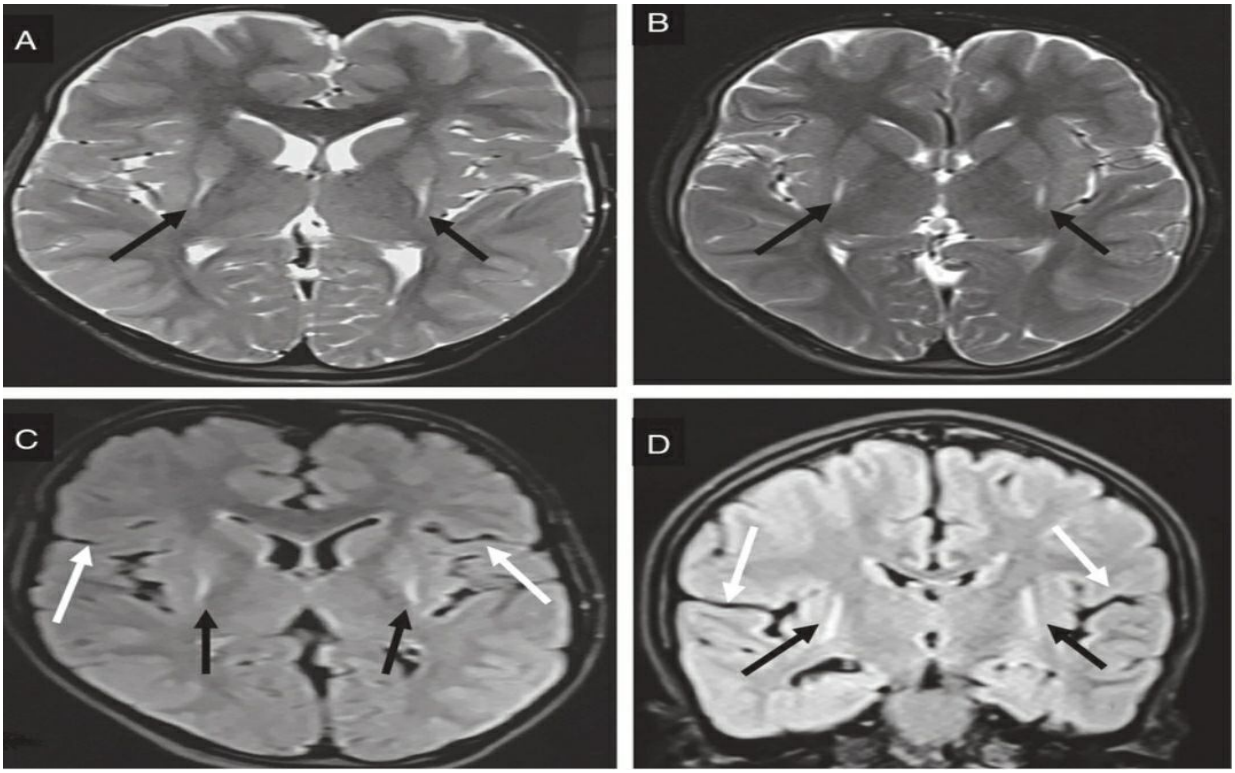

Figure 13: MRI T2 axial of case (A) and case (B) showing bilateral symmetrical hyperin tensities in posterior putamen with posterior putaminal atrophy.*Axial FLAIR (C) and coronal FLAIR (D) no widening of sylvian fissure and no fronto temporal lobe atrophy that is usual finding in glutaric* aciduria (Shaik *et al*., 2019).

III.2.4. Clinical evaluation

This includes the patient's medical history, physical examination, and assessment of symptoms and clinical signs (Patient's medical history and physical examination that may indicate the disease) (Tuncel *et al*., 2018).

The serum C5DC, C5DC/C8 ratio, and urinary GA values of patient sintervention are summarized in Table 2. All 101 patients received at least one MS/MS test, and 89 patients were available for GC-MS analysis, with 78 patients identified as high excretors. (Tuncel *et al*., 2018)

There were significant differences in the C5DC concentration (0,02~0,25 µ mol/L), C5DC/C8 ratio, and urinary GA levels in each of the patient groups following treatment. In addition, when these variables were compared between the NBS (newborn screening and clinical groups, significant differences were noted in all of them with the exception of the C5DC value in NBS patients. On comparing the NBS and clinical groups, only a significant difference in the C5DC values after treatment could be identified. The C5DC levels of three patients were normal at their initial evaluations and their GA1 diagnosis were based on an increased C5DC/C8 ratio, which was then further confirmed by a GCDH gene test (Gelener; 2020).

Table 2: Levels of C5DC in the blood, C5DC/C8 ratios and urinary GA in each of the three groups (Gelener; 2020).

	C5DC (µ mol/L)	**C5DC/C8**	**GA5(mmol/mol Cr)**
Reference range	0.02~0.25	0.10~2.50	0~8
All patients	0.92(0.11~5.13)	22.04(1.6~218)	562.76 (0.12~4.51)
NBS patients	1.64(0.11~3.2)	19.81(1.6~214)	547.51(1.92 ~2.14)
Clinical patients	0.83(0.13~5.13)	22.29(2.58~218)	578.5(0.12~4.415)
P (NBS – Clinial)	0.148.	0.973	0.702
P(all patients)*	0.012	0.001	0.001
P(NBS)	0.477	0.011	0.012
P(Clinical)*	0.014	0.011	0.001

*P value for each group before and after treatment.

Test Definition: C5DCU C5-DC Acylcarnitine, Quantitative, Random, Urine

An isolated elevation of glutaryl carnitine (C5-DC) in plasma or newborn screening blood spots is indicative of a diagnosis of glutaric aciduria type 1 (GA-1), also known as glutaric acidemia type 1. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase. Diagnostic testing through acyl carnitine analysis, including the evaluation of C5DC in urine, is useful in determining if a patient has GA-1. Urinary excretion of C5-DC serves as a specific biochemical marker of GA-1, even in cases of low excretion where patients are affected but exhibit normal levels of glutaric acid in urine (Miller *et al*; 2021).

III.3. Differential Diagnoses for GA1

Diagnostic algorithm for glutaric aciduria type I (see Fig14), Newborn screening for GA-I is performed using MS/MS. In low excretor cohorts with known mutations, GCDH gene mutation analysis should be considered as alternative method (dotted line). Note that in these patients treatment should be started after the identification of two disease-causing mutations. Selective screening should be initiated if the diagnosis of GA-I is suspected clinically or there is a positive family history. Note that a few patients with a low-excreting phenotype may show

(intermittently) normal urinary excretion of 3-OH-GA (and GA). If an individual shows normal 3-OH-GA (and GA) concentrations in urine (or other body fluids) but presents with highly suspicious signs and symptoms for GA-I, further diagnostic studies should be considered but the decision should be made based on the individual circumstance. Comment on mutation and enzyme analysis: Since GCDH gene analysis is more broadly available than GCDH enzyme analysis, and the identification of two disease-causing mutations not only confirms the diagnosis but also enables accurate genetic counselling and prenatal diagnosis, we recommend starting with GCDH gene analysis. However, depending on local availability and experience, GCDH enzyme analysis could be performed first (Shadmehri; 2018).

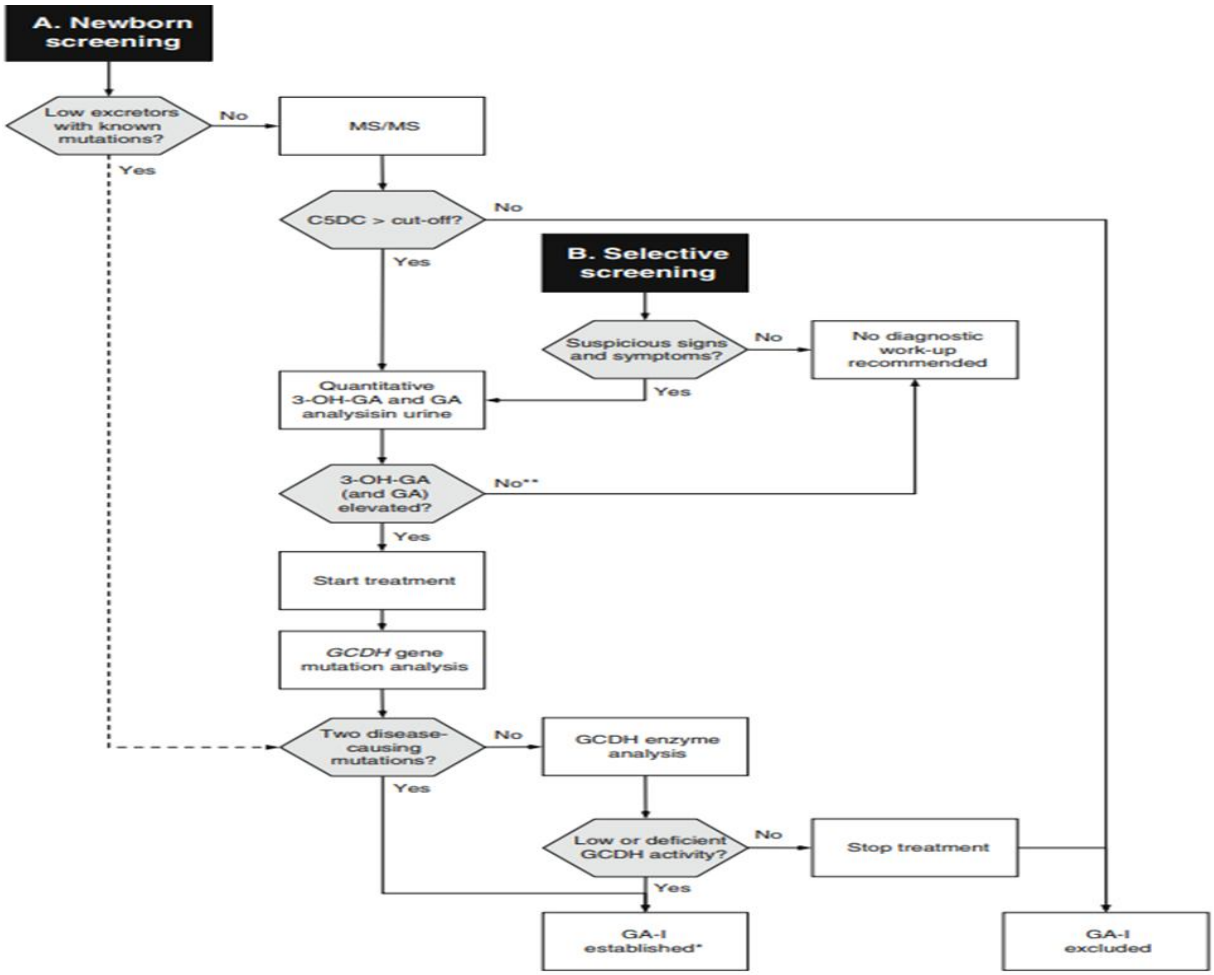

Figure 14: Diagnostic algorithm for glutaric aciduria type I.A, Newborn screening for GA-I. B, Selective screening should be initiated if the diagnosis of GA-I (Shadmehri; 2018).

Chapter IV:

treatment of Glutaric aciduria type I

IV. Treatment

Kolker *et al*. (2007) have provided recommendations for managing type I glutaric aciduria. In the event of acute decompensation, hospitalization is necessary to implement an emergency protocol. This protocol aims to restart anabolism through carbohydrate and lipid intake, reduce accumulated levels of glutaric acid and 3-hydroxyglutaric acid by administering a protein-free diet for 24 to 48 hours, and enhance physiological elimination while preventing secondary carnitine deficiency through the administration of IV carnitine, such as Levocarnil® (dosage: 100 mg/kg/day) (Kölker *et al.,* 2011)**.**

IV.1. Historical review of attempted foe therapies GA-I

Treatment of GA-I can be broadly divided into two categories: pharmacologic and dietary. These therapies have been attempted individually and in combination.

IV.1.1. Pharmacologic Therapy

IV.1.1.1. Carnitine

Carnitine is an important transport substance in the human body, mainly absorbed through the diet. Carnitine attaches to glutaryl-CoA (see Figs. 15), which is formed inside cells to produce glutaryl carnitine. Glutaryl carnitine is released into the blood and then excreted in the urine by the kidneys (Dr. Nikolas *et al.*, 2018).

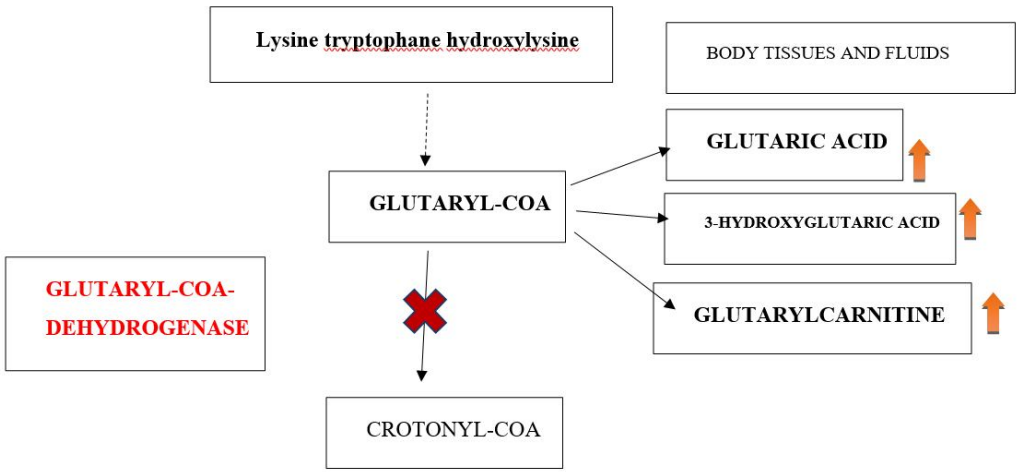

Figure 15: Cause of type glutaric aciduria type I (Dr. Nikolas *et al*, 2018).

Glutaryl-CoA dehydrogenase catalyzes a particular step in the common final catabolic pathways of the amino acids lysine, hydroxylysine and tryptophan. (Leandro, J; Houten, S. M, 2020)
In terms of quantity, the degradation of lysine is greater than that of tryptophan and hydroxylysine. In type I glutaric aciduria, the congenital enzyme abnormality leads to an

accumulation of specific metabolic products (glutaric acid, 3hydroxyglutaric acid, glutaryl carnitine) (Li *et al.*, 2021).

This is a physiological detoxification strategy to reduce the accumulation of harmful metabolic products and increase the available amount of free coenzyme A (CoA), a substance important for many metabolic reactions (see fig 16) (Dr. Nikolas *et al.*, 2018).

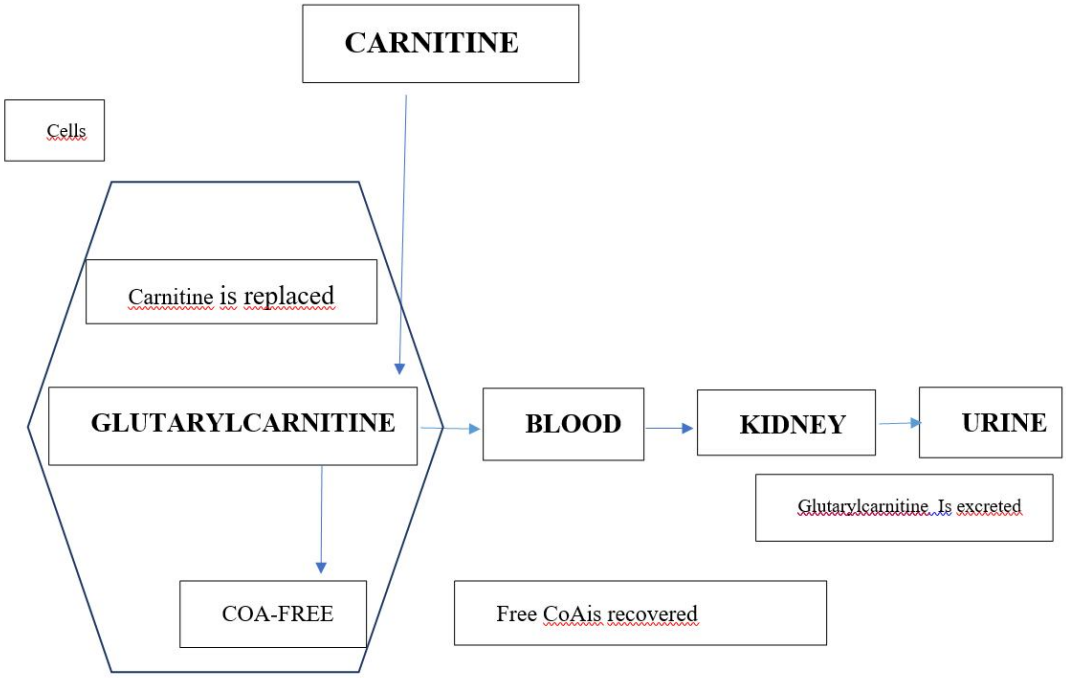

Figure 16: Carnitine-based treatment (Dr. Nikolas *et al.*, 2018)

Accumulated glutaryl-CoA attaches itself to the transport substance carnitine, allowing it to leave the cells as glutaryl carnitine and subsequently be excreted in the urine.
This releases CoA into the cell, making it available for other metabolic reactions.
However, the body loses a great deal of carnitine during this detoxification reaction. The loss is compensated for by carnitine juice.

However, the body loses so much carnitine during this important reaction that dietary intake is insufficient to compensate for this loss, resulting in a carnitine deficiency. Untreated GA-I sufferers often have a secondary plasma carnitine deficiency (Lipkin *et al.*, 1988; Wang, 2014). Carnitine conjugates with GA to form the non-toxic glutaryl carnitine, and may reduce the intracellular CoA pool through the accumulation of glutaryl-CoA (Seccombe *et al.*, 1986).

The resulting secondary carnitine deficiency can be overcome by oral carnitine supplementation. L-carnitine supplementation reduces the risk of striatal damage when GA-I is diagnosed early

(Couce *et al*., 2013; Viau, 2012), and reduces mortality in symptomatic patients (Kölker *et al*., 2006). A recent study also suggests an antioxidant effect of L-carnitine administration (Guerreiro *et al*., 2018).

IV.1.1.1.1. Carnitine dose

Life long carnitine supplementation is therefore generally recommended (Kölker *et al*., 2006; Strauss, 2003; Bjugstad, 2000; Hoffmann, 1996).

The initial dose (before the age of 6) is 100 mg/kg oral L-carnitine in three doses. In some children, carnitine administration may cause strong body odor (fishy) and diarrhea (Boy *et al*., 2017; Kölker, 2007; Strauss, 2003). An annual carnitine dosage is performed to check compliance with treatment and that levels are within the normal range. In adults and children over 6 years of age, the initial dosage may be reduced to 30-50 mg/kg/day (Boy *et al*., 2017). During periods at risk of metabolic decompensation, the dose of carnitinemay be doubled.

IV.1.1.2. Riboflavin (VITAMIN B2)

The glutaryl-CoA dehydrogenase enzyme affected by type I glutaric aciduria needs riboflavin (vitamin B2) as a cofactor to function properly. For this reason, a daily dose of riboflavin was administered in the hope of reducing the activity of the defective enzyme. However, no recent study has been able to prove that riboflavin actually has a positive influence on the course of the disease. This can probably be explained by the fact that the defective enzyme can only very rarely be sufficiently stimulated by riboflavin. There is currently no reliable method for testing riboflavin sensitivity, or to predict it on the basis of molecular genetic studies (Dr. Nikolas *et al*., 2018).

Riboflavin responsiveness in GCDH deficiency appears to be rare (Chalmers *et al*., 2006).

IV.1.1.3. Symptomatic treatments (especially management of dystonia)

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

IV.1.1.3.1. Baclofen:

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

IV.1.1.3.2. Benzodiazepines

Diazepam and clonazepam have been successfully used in treating dystonia (Hoffmann *et al*., 1996; Kyllerman*et al.*, 1994). Dosages should be administered according to general recommendations. In some patients suffering from a high variability of severity of symptoms, they tachyphylaxis (Hoffmann *et al*., 1996; Kyllerman *et al*., 1994).
an be adjusted daily within a given range. Intermittent treatment may be required to prevent

IV.1.1.3.3. Anticholinergic drugs

Trihexyphenidyl is effective in treating dystonia (Burlina *et al*., 2004). High doses of the drug can be reached only if trihexyphenidyl is increased slowly. Adverse effects such as blurred vision and dry mouth are temporary. Memory deficit and confusion usually persist and require dosage reduction. Adverse effects are encountered more frequently in adults than in children (Kimura *et al*., 1999).

IV.1.1.3.4. Botulinum toxin

Botulinum toxin type A (BT-A) has recently been reported as alternative therapy for focal dystonia in an affected girl (Burlina *et al*., 2004).

An additional nine patients (aged 7–21 years) have been successfully treated with BT-A (S. Kölker, personal communication, 2006).

BT-A therapy is not or is only partially efficacious if started after the manifestation of significant joint contractures.

BT-A should be administered by a neurophysiologist or neurologist with experience of this treatment. Some patients can develop immunity against the toxin, precluding further therapy; therefore, BT-A is usually administered every 3 months to minimize the formation of antibodies against the toxin (Jankovic., 2004).

IV.1.1.3.5. Antiepileptic therapy

Dystonic movements may be mistaken as seizures. No study has investigated the comparative efficacy of antiepileptic drugs in GCDH deficiency. However, phenobarbital, phenytoin, carbamazepine, topiramate, and lamotrigine have all been used (McClelland *et al.,* 2009).

IV.1.1.3.6. Neurosurgery

Neurosurgical interventions have been performed in a small number of affected patients with arachnoid cysts and subdural hemorrhage (HedlundGL *et al*., 1991; Lütcherath, 2000; Martinez-Lage, 1994; Woelfle, 1996).

The majority of these patients had a poor neurological outcome or had no significant neurological improvement. In particular, in undiagnosed patients who do not receive specific metabolic treatment, neurosurgical interventions can precipitate an encephalopathic crisis. Subdural hemorrhage may regress without neurosurgical intervention if metabolic treatment is intensified (E. Naughten, personal communication, 2005).

IV.1.2. Dietary Therapy

IV.1.2.1. Introduction

Dietary treatment of type I glutaric aciduria should be based on general criteria according to age and daily nutritional requirements. This is absolutely essential for normal growth and development. The diet follows the dietary recommendations of national and international expert societies, which describe the minimum requirements of a growing child according to age (Dr. Nikolas *et al*., 2018).

The main aims of treatment are to reduce lysine oxidation and improve physiological detoxification of glutaryl-CoA, thus avoiding excessive GA accumulation (Boy *et al*., 2013).

IV.1.2.2. The Principles of the Plan

Nutritional management includes the following elements:

A controlled protein diet specifically excluding lysine-rich foods. This involves a diet combining natural proteins and a lysine-free, tryptophan-poor amino acid blend (AAM),

- which is then adapted according to clinical progress and metabolic controls. This low-lysine diet should be maintained until the age of 6, after which the risk of neurological decompensation has never been reported (protein intake according to Dewey *et al*., 1996).
- Sufficient energy intake, adapted to the patient's age, level of physical activity, and clinical situation (dystonia, etc.). This energy intake must enable permanent anabolism to meet the growth needs of children and the maintenance needs of adults. It must be

sufficient to avoid protein catabolism, which can lead to decompensation (Jurecki *et al*., 2019).

- Carnitine supplementation, to be increased in situations at risk of decompensation.
- Implementation of an emergency protocol during intercurrent episodes and high-risk situations to prevent catabolism and minimize CNS exposure to toxic metabolites (Boy *et al*., 2023).

IV.1.2.3.3. Practical Realization of the Diet

IV.1.2.3.1. From 0 to 6 years old

IV.1.2.3.1.1. The diet nutritional

The diet must be implemented by a multidisciplinary healthcare team specializing in MHM (doctors and specialized dieticians), ideally trained in therapeutic education. Training begins during the initial hospitalization and continues with each consultation. Lysine intake is determined according to the patient's age (Table 3; Figs 17) The diet is based on three lists of common foods, indexed by their lysine content:

- Forbidden foods: containing too much lysine, e.g., meat, fish, eggs, legumes (from 500 mg to 2472 mg LYS per 100 g).
- Foods to control: providing the tolerated amount of lysine essential for maintaining protein synthesis. These are mainly fruits, vegetables, starchy foods, milk, and dairy products (20 mg to 450 mg LYS per 100 g).
- Uncontrolled foods: due to their absence or low lysine content (fats, sweet products), to which hypoprotein foods are added (Souci *et al*., 1994).

Table 3: nutritional needs according to age (Souci *et al.,* 1994)

Treatment	Units	Age0-6 months	7-12 months	1-3 years	4-6 years	>6 years
Low lysine diet lysine (from natural proteins)	Mg/kg/day	100	90	80-60	60-50	Controlled protein intake based on natural proteins with low lysine content, avoiding lysine-rich foods
Amino acid mixtures (protein equivalents)	g-kg-day	1.3-0.8	1-0.8	0.8	0.8	
Energy	Kcal/kg/day	100-80	80	94-81	86-63	

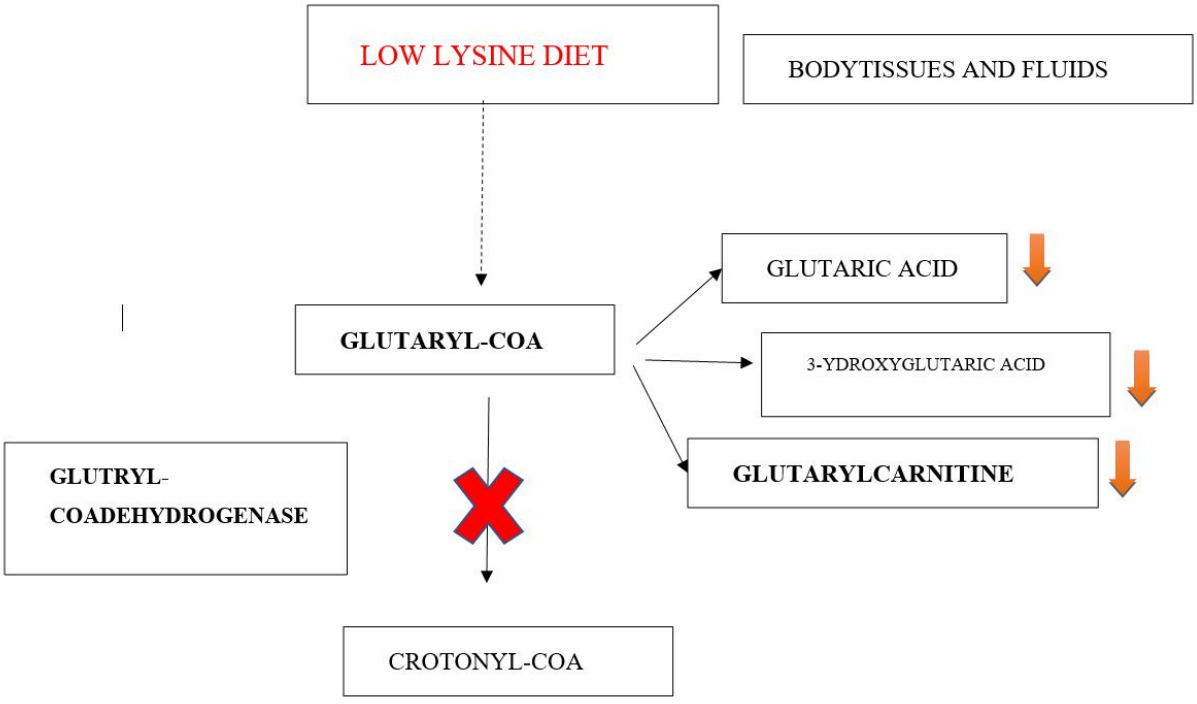

Figure 17: Low-lysine dietary treatment lysine content (Dr. Nikolas *et al*., 2018).

In terms of quantity, lysine is the main amino acid precursor of the metabolic products that accumulate in the case of type I glutaric acid type I (glutaric acid, glutaric acid 3-hydroxyglutaric acid, glutaryl carnitine).limiting lysine intake in the diet reduces the accumulation of these metabolic products in the body, particularly in thebrain.

IV.1.2.3.1.2. Breast feeding

Breastfeeding is the most physiological form of nutrition for newborns and infants. The lysine content of breast milk is 86 mg/100mL. There is little published experience of breastfeeding in AG-I, but it is recommended in the latest European guidelines and could be carried out in the same way as in phenylketonuria (either every other feeding [alternating breastfeeding - AAM] or starting feeding with AAM and supplementing with breastfeeding) (Huner *et al*., 2005; Boy *et al*., 2017).

The special formula is given at the start of the meal. The infant can then be breastfed until satiated. As the quantity of breast milk and thus the lysine intake are estimated, regular monitoring of weight gain and growth, and measurement of plasma amino acid levels are necessary. This approach is widely used and considered safe (Boy *et al*., 2018).

However, if a precisely calculated daily lysine intake is indicated, the amount of breast milk should be measured. The amount of breast milk ingested by the infant is determined by weighing the infant before and after breastfeeding (test weighing). The results are recorded and added up over a 24-hour period. The indicated quantity of breast milk is given at the start of the meal, followed by the special tryptophan-reduced lysine-free formula as required (Boy, *et al*., 2023).

A sufficient reduction in lysine intake is already achieved when the daily intake of breast milk is reduced by around 20%. This means that the infant receives 20% of the usual amount of drink with the special tryptophan-reduced lysine-free formula, and 80% with breast milk (van Rijn *et al*., 2003).

The table below shows the proportion of special formula and breast milk in the total quantity of drink in relation to body weight.

Table 4: dosage the special preparation (Boy *et al*; 2018).

Weight(Kg)	Special peparation (Ml)	Breast milk estimated quantity(Ml	Total quantity of drink estimated quantity(Ml)
3 - 3,5	100	400	500
3,6 – 4,0	120	450-500	600
4,1 – 4,5	140	550-600	700
4,6 – 5,5	160	600-650	800
5,6 - 6	180	700-750	900
>6	200	800	1000

IV.1.2.3.1.3. Feeding

Infant formulas contain more lysine than breast milk, which is why the proportion of special formula is higher in non-breast-fed children. The specified lysine dose is achieved by feeding a calculated amount of formula. The pre-determined amount of formula is given at the beginning of the meal, followed by special formula as required. Once all the formula has been used, only the special formula is fed at all other meals (Boy *et al*., 2018).

IV.1.2.3.2. Over 6 Years Old

Clinical outcome after the age of 6 varies from patient to patient. Acute striatal damage or insidious onset has been described before the age of 6. Nevertheless, patients with late onset, starting in adolescence or adulthood, have been described. There are also reports of extra-striatal involvement on MRI, of uncertain clinical significance (Harting *et al*., 2009). As the link between this evolution and diet has not been demonstrated, the diet can be extended after the age of 6, but a controlled protein diet combined with exclusion of lysine-rich foods is still recommended. On the other hand, the maintenance or discontinuation of lysine- and tryptophan-poor substitutes (AAM) and hypoprotein foods will have to be assessed on a case-by-case basis by the competent teams. In general, these are no longer useful in the light of this enlargement (Boy *et al*., 2017).

The quantity of natural proteins will be established according to the EFSA recommendations (EFSA Dietary reference values for the EU.), respecting a ratio of animal and vegetable proteins of 50% - 50%.

In this age group, foods can be classified into 3 categories:

- Foods Contraindicated: containing excessive amounts of lysine, such as certain nuts and seeds (> 800 mg LYS/100 g).
- Foods to be Controlled: ensuring that the body has sufficient quantities of all important nutrients. These include milk or equivalent dairy products, meat, fish, eggs, and legumes.
- Non-controlled Foods: providing calories for emergency diets. These include starchy foods, vegetables, fruit, fats, and sweets.

This diet will be established and regularly re-evaluated by the specialist MHM team (doctors and dieticians) in charge of the patient (Protocole National de Diagnostic et de Soins (PNDS) Acidurie glutarique type 1/ April 2021).

IV.1.2.3. The Different Types of Diet

IV.1.2.3.1. Before Age 6

The Cruising Regime It provides the quantity of lysine required for growth and normal protein metabolism. It is adapted to the patient's age. The calculation of this intake must be carried out by specialized teams. Energy intake must be sufficient. Intake should cover the child's needs, and should be re-evaluated regularly according to age and clinical condition.

The Emergency Regime An emergency diet is prescribed:

- At diagnosis if made during acute decompensation.
- In the event of metabolic decompensation.
- To prevent acute decompensation of metabolic disease (catabolic risk situation: intercurrent infection, fever, surgery, etc.).

Emergency diets should be administered in hospital for a short period (48 hours maximum). Prolonged use of such a diet can be deleterious (major risk of undernutrition) (Kölker *et al.*, 2011).

For each episode of decompensation (or at risk of decompensation), the referring physician assesses the place and duration of hospitalization, in the local hospital or in the referral hospital.

This emergency plan includes:

- Total elimination of natural protein intake (elimination of lysine intake). Natural protein intake is resumed (50% then 100%) within 24-48 hours of the start of the emergency diet.
- Maintaining MAA intake (Boy *et al*., 2021).

The energy intake must be increased to 120% of the usual energy intake, with 50-60% of carbohydrates in the Total Energy Intake (TEI) and 40-50% of fat in the TEI. In order to achieve this energy increase, the following products must be used:

- Low protein foods.
- Fats and sugars, commercially available in various forms.
- Maltose dextrine.
- Fats such as oils and lipid emulsions.
- Carbohydrate-lipid powders with or without VMO.

This emergency diet can be administered orally and coupled with enteral nutrition if necessary. Continuous enteral nutrition may be recommended to increase energy intake and combat endogenous catabolism. In the event of digestive intolerance, a carbohydrate-lipid infusion (not forgetting VMOs) may replace enteral nutrition (Bjugstad *et al*., 2000; Kölker *et al*., 2006; Strauss *et al*., 2003).

The Semi-Emergency Regime It can be used, either per os or as enteral nutrition, following the emergency diet, to gradually restore lysine intake. Lysine intake is reduced by half compared with the cruising diet, while trying to maintain a good distribution of natural proteins throughout the day. Energy intake is always higher than on the cruising diet, so as to come close to the minimum 120% of Nutritional references for the population (RNP) (Acosta *et al*., 1997).

IV.1.2.3.2. After 6 Years

The Cruising Regime After the age of 6, the low-protein diet can be extended, according to the recommendations given in the table below.

These recommended quantities ensure that the body has sufficient quantities of all important nutrients. Thus, Amino acidmixture (AAM) may no longer be necessary if natural protein intake covers the patient's specific needs.

Table 5: Recommended average quantities of animal products for schoolchildren and adolescents by optimix (Protocole National de Diagnostic et de Soins (PNDS) Acidurie glutarique type 1/ April 2021)

animal products	Quantitie sordered	6 y	7 -9 y	10 -12 y	13 -14 y	15 -18 y
milk, dairyproducts	ml/ day g/ day	350	400	420	425 f 450 m	450 f 500 m
meat, charcuterie	g/ day	40	50	60	65 f 75 m	75 f 85 m
eggs	piece/ week	2	2	23	23(f /m)	2 -3 (f/m)
fish	g/ week	50	75	90	100(f/m)	100 (f/m)

The Regime for Emergency Situations

In situations where there is a risk of intense catabolism, it is recommended to reduce protein intake and increase calorie intake by:

- Transient cessation of animal proteins.
- Increased intake of uncontrolled foods, especially those rich in carbohydrates and fats. In the event of eating difficulties (without digestive problems), carbohydrate-lipid intake via NE is recommended. In the event of digestive intolerance, a carbohydrate-lipid infusion replaces the NE (Protocole National de Diagnostic et de Soins (PNDS) Acidurie glutarique type 1/ April 2021).

Conclusion

Conclusion

In conclusion, glutaric aciduria type 1 is a rare metabolic disorder characterized by a deficiency in the enzyme glutaryl-CoA dehydrogenase, resulting in the accumulation of toxic levels of glutaric acid and other metabolites in the body. This can lead to a range of neurological symptoms, including developmental delays, movement disorders, and seizures. Early diagnosis through newborn screening and appropriate management strategies, such as dietary modifications and medication, are essential in mitigating the symptoms and preventing long-term complications.

Regular monitoring by a multidisciplinary healthcare team is crucial in optimizing the care and quality of life for individuals with glutaric aciduria type 1. Further research into the genetic and biochemical mechanisms underlying this disease, as well as the development of targeted therapies, is needed to improve outcomes and quality of life for individuals affected by glutaric aciduria type 1.

Increased awareness and understanding of this rare disorder among healthcare professionals, families, and the general public are also important in ensuring timely diagnosis and appropriate management of affected individuals.

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