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Simplified Approach to Glutaric Acidurias: A Mini-Review

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Abstract

Inherited metabolic diseases (IMDs), comprise a large class of genetic diseases affecting the metabolism. Expanded newborn screening from dried dried blood spot (DBS) samples for inborn errors of metabolism has increased the detection of metabolic disorders in asymptomatic newborns and reduced the morbidity and mortality by early interventions. Organic acidurias (OADs) arise from the defects in the intermediary metabolic pathways of carbohydrate, amino acid and fatty acid oxidation, leading to the accumulation of organic acids in tissues and their subsequent excretion in urine. Glutaric acidurias are a group of OADs which have three major types with different genetic mutations affecting different metabolic enzymes. In this mini-review we will compare three types of GA and their genotypes, symptoms, diagnosis, and treatments will be discussed briefly.

Inherited metabolic diseases (IMDs), often referred to as inborn errors of the metabolism (IEM), comprise a large class of genetic diseases affecting the metabolism. The prevalence of these diseases, all together, is estimated to be at least one in every 1,500 individuals in the world[1]. Except for the X-inherited ones there is no difference in the incidences of IMDs between two sexes[2]. Some metabolic disorders can be diagnosed through routine newborn metabolic screening tests at birth while others are identified only after the patient develops symptoms of a metabolic disorder. Newborn screenings for metabolic disorders (NBS) are conducted in many of the developed and developing countries worldwide. The main goal of newborn screening for IEM is to reduce morbidity and mortality through early interventions such as dietary and pharmacological treatments. In recent years, expanded NBS used in tandem mass spectrometry has increased the detection of many IEMs in asymptomatic newborns. The definite diagnosis of such patients is achieved through genetic analysis. Treatment for IMDs depends on the type and severity of the disease, and since there are so many types of IMDs, treatments may vary from dietary restrictions and supplements to liver transplants[1].

Organic acidurias (OADs) are an important class of IMDs arising from the defects in the intermediary metabolic pathways of carbohydrate, amino acid and fatty acid oxidation, leading to the accumulation of organic acids in tissues and their subsequent excretion in urine[2]. More than 100 different organic acids are excreted in urine under these conditions[2]. The major organic aciduria disorders include propionic aciduria (PA), methyl malonic aciduria (MMA), branched chain organic aciduria, glutaric acidurias (GAs) and multiple carboxylase deficiencies[2,3]. Organic acidurias usually present with hyperammonemia with a high anion gap metabolic acidosis, in addition to hypoglycemia and ketonuria. The

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major clinical features include developmental and mental retardation, cardiac dysfunction, lethargy, coma, seizures, hypotonia, failure to thrive, hepatomegaly, and respiratory distress[2].

Glutaric acidurias are a group of OADs which have three major types with different genetic mutations affecting different metabolic enzymes and all three having an autosomal recessive inheritance. In this mini-review we will compare three types of GA and their symptoms, diagnosis, and treatments will be discussed briefly in the light of literature.

Glutaric Aciduria Type I (GA-I, OMIM 231670, GARD 6522, ORPHA 25):

Glutaric aciduria type I (GA-I) is an autosomal recessive organic aciduria caused by glutaryl-CoA dehydrogenase (GCDH) deficiency with an estimated overall prevalence of 1 in 100,000 newborns. GA-I is considered to be a neurological disorder and a cerebral organic aciduria[4]. Since the initial description of two index patients in 1975 and 2011, only 500 cases have been reported worldwide[5,6]. The GCDH gene which plays a key role in this disorder is localized on chromosome 19p13.2, and a deficiency in this particular gene results in an impaired metabolism of L-lysine, L-hydroxylysine and L-tryptophan, leading to the accumulation of 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC)[7] **(Table 1).** Increased urinary concentrations of 3-OH-GA is the most sensitive biochemical marker for diagnosis and the diagnostically relevant metabolite is elevated C5DC in dried blood spot (DBS) screening. However since NBS in newborns reflects the metabolic state of the mother and the infant, NBS laboratories should be aware that elevated C5DC concentrations may indicate maternal GA-I[8,9]. In addition, some laboratories are also using ratios of C5DC to other measured acylcarnitines such as C5DC/C8 or C5DC/C16 in GA-I diagnosis[10,11] **(Table 1).** Aside from the primary disease maternal GA-I cases can be diagnosed based on the findings in their offspring. Women with GA-I can be diagnosed retrospectively following a positive newborn screening test in their babies due to the elevated metabolites that can easily cross the placenta from maternal blood[12]. Babies are mainly asymptomatic or show only transient mild neurologic symptoms and although not treated they are not expected to develop metabolic complications during pregnancy, delivery or the puerperium[13,14].

For further diagnosis, glutaryl-CoA dehydrogenase

Table 1. Genotypes, Phenotypes, Laboratory Findings and Possible Treatments of Glutaric Acidurias

GA Type	Prevalance	Gene	Inheritance	DBS Results	Urine Organic Acid Results	Clinical Symptoms	Treatment	References
GA Type1	1:100000	GCDH	AR	Elevated C5DC C5DC /C16 Ratio C5DC/C8 Ratio	Elevated Glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), Glutaconic acid (less frequently)	Macrocephaly Dystonia, Seizures Delayed motor skills, Metabolic acidosis	low lysine and increased glucose intake diet L-Carnitine Riboflavin Baclofen and Benzodiazepines	6,11,15,34
GA Type2	1:200000	ETFA ETFB ETFDH	AR	Elevated Short/medium/long chain acylcarnitines From C4 to C18	Elevated Glutaric acid, Lactic acid, Ethylmalonic acid, Butyric and Isobutyric acid, 2-methyl-butyric acid, Isovaleric acid, Suberic acid, Sebacic acid and Adipic acid	Respiratory failure, Cardiomyopathy, Hypotonia, Metabolic acidosis, Hypoglycemia, Congenital anomalies, Lethargy	Low-fat diet, Avoidance of fasting, Riboflavin, L-carnitine and glycine, Sodium-D,L-3 hydroxybutyrate (NaOHB)	18,21,22,26,34
GA Type3	unknown	SUGCT	AR	Not detectable by bloodspot acylcarnitine-based newborn screening	Persistent isolated elevation of glutaric acid (GA)	Not spesific Mostly asymptomatic	No Therapy/Symptomatic Therapy	27,28,30,31, 34

stearoylcarnitine; GCDH: Glutaryl-CoA dehydrogenase; ETF: electron transfer flavoprotein; ETFDH: electron transfer flavoprotein dehydrogenase; SUGCT: succinyl-CoA:glutarate-CoA transferase; AR: Autosomal recessive

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activity in cultured fibroblasts can be measured and mutation analysis carried out on genomic DNA[15]. To date, two biochemically defined subgroups of GA-I patients have been described based on the urinary metabolite excretion of GA, i.e., low and high excretors[16]. Low excreting patients have the same risk of developing striatal injury as the high excretors and should not be considered to have a "mild" clinical phenotype[17].

The initial progression of clinical symptoms in cases of GA-I is slow; hence GA-I is frequently left undiagnosed until an acute metabolic crisis occurs. A child suffering from GA-I usually presents with macrocephaly which is found in 75% of GA-I patients during infancy[18,19]. Neuroradiologic findings in GA-I may occur in some cases even before the onset of neurologic symptoms. The most striking finding at brain imaging in GA-I is the presence of very wide cerebrospinal fluid (CSF) spaces anterior to the temporal lobes and within the sylvian fissures These findings although not present in all cases might help the doctors recognize the disease in an asymptomatic child, evaluated for macrocephaly, before irreversible brain damage has developed[20].

Clinical presentations with acute encephalopathic crises are seen mostly between 6 and 18 months and induced by febrile illness, fasting, or immunization. Dystonia and extrapyramidal symptoms such as athetosis, seizures, and intellectual disability may be the other signs in GA-I. However some patients with GA-I remain asymptomatic, even in the adulthood[21]. Glutaric aciduria type I suspicion may be based on typical risk factors such as family history, consanguineous marriage, and deceased sibling. Further laboratory findings may include severe acidosis, ketosis, hyperammonemia, and abnormal liver function tests. The early diagnosis of GA-I is essential, since the metabolic symptoms can be usually prevented by carnitine supplementation and a diet that is low in lysine and tryptophan to reduce glutaric acid production, and also may include supplementation with L-carnitine, riboflavin[15]. GA-I is a good candidate for NBS, and the aim of NBS in GA-I cases is to reduce the risk of irreversible neurological disease following the striatal injury[4].

Glutaric Acidemia Type II (GA-II, OMIM 231680, ARD 6523, ORPHA 26791)

Glutaric aciduria type II (GA-II) also known as multiple acyl-CoA dehydrogenase deficiency (MADD) is an autosomal recessive disease caused by a defect in electron transfer flavoprotein (ETF) or ETF dehydrogenase (ETFDH), resulting in deficiencies in multiple acyl-CoA dehydrogenases, such as short-, medium-, and long-chain acyl CoA dehydrogenases[22]. GA-II is mainly caused by homozygous or compound heterozygous mutations in the ETFA, ETFB or ETFDH genes. Mutations in ETFA and ETFB are usually associated with the neonatal forms, whereas

ETFDH mutations often present as late-onset forms[23]. There are three main clinical phenotypes of GA-II: First, the neonatal form with congenital anomalies, second, the neonatal form without congenital anomalies; and third, the late onset form with myopathic phenotype, and rarely, metabolic acidosis[24]. Muscle weakness is a common finding in late-onset presentations of GA-II. Although muscle biopsy is usually invaluable in the diagnosis of myopathies, histological findings of lipid deposition can be an initial clue for the diagnosis of GA-II in patients with myopathy[22,25].

The clinical presentation and disease onset may vary depending on the location and nature of the mutations[26]. Many patients with GA-II present with hypotonia, tachypnea, hypoglycemia, and, often, neonatal death, or with a Reye's syndrome-like illness.

Acylcarnitine analysis in tandem mass spectrometry is a preferred diagnostic tool for GA-II cases. Acylcarnitine profiling by tandem mass spectrometry, screening of serum or dried blood spot samples characteristically shows increased concentrations of short-, medium-, and long-chain acylcarnitines[26]. A urinary organic acid analysis by GC/MS shows an increased excretion of characteristic compounds such as adipate, suberate, sebacate, glutarate, 2-hydroxyglutarate, ethylmalonate or isovalerylglycine, as the corresponding metabolites derived from defective steps[27]. In late-onset cases, the elevation of acylcarnitine levels may be mild and atypical, or detectable only during an acute episode. Under these circumstances, genetic screening is the key to establish a definitive diagnosis[23]. Furthermore, novel compound heterozygous mutations in ETF have been described in many individual cases in the literature[23,28].

The conventional treatment of GA-II, including a protein- and fat-restricted, carbohydrate-rich diet, and riboflavin, glycine, and L-carnitine supplementation, may be effective in mildly affected patients, however, in some cases results can be disappointing. Riboflavin is the precursor of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), and is considered to be the main therapeutic agent, due to its favorable effect on flavin-dependent mitochondrial enzymes and result in a dramatic improvement in the muscular strength, tone and trophism as well as in the aerobic performance[29]. A racemic mixture of sodium D,L-3-hydroxybutyrate (NaHB) is a promising treatment option aiming to replace the deficient endogenous ketone body production which is needed not only for energy supply, but also for the synthesis of complex cell and tissue components such as myelin in the central nervous system[30]. Cardiomyopathy is a frequent cause of death in MADD which warrants experimental treatment. D,L-3-hydroxybutyrate is an additional therapeutic option for cardiomyopathy and cerebral dysfunction in severe fatty acid oxidation defects. Treatment with D,L-3-

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hydroxybutyrate is safe and effective and not associated with any notable adverse side-effects[28, 31].

Glutaric Aciduria Type III (GA-III, OMIM 231690; GARD 12469; ORPHA 35706)

Glutaric aciduria type III (GA-III) is often considered a "non-disease" that is caused by mutations in the succinyl-CoA:glutarate-CoA transferase (SUGCT) gene, that produces deficiency of succinate-hydroxymethylglutarate CoA-transferase, and provoking the decreased conversion of free glutaric acid to glutaryl-CoA with no symptoms. It remains less well known, characterized or understood than other types of GA[32, 33]. The succinyl-CoA:glutarate-CoA transferase gene that plays a role in this disorder is localized on chromosome 7p14.1[34]. GA-III is also an autosomal recessive disorder like the other GAs. Glutaryl-CoA oxidase deficiency is a peroxisomal disorder leading to glutaric aciduria and the prevalence is unknown[34]. With no known biomarker other than notable glutaric aciduria without elevation of any other markers of GA-I or GA-II, and an increased glutaric acid excretion following lysine loading, GA-III is thought to be a "diagnosis of exclusion," following suspicion based on clinical manifestations or metabolite profiles[32].

Bennett et al. first described the case of GA-III, a one year-old girl with failure to thrive, beta-thalassemia, abnormal urinary amounts of glutaric acid and a lack of detectable activity of peroxisomal glutaryl-CoA oxidase[35]. Later on, Knerr et al. reported three cases with no distinctive phenotype, and Sherman et al. also reported three healthy children who excreted large quantities of glutarate but low 3-hydroxyglutarate, consistent with the phenotype of GA-III based on the screening of Amish infants, who received no treatment and remained healthy for more than 15 years[36,37].

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