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Glutaric Aciduria Type I: Overview

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Glutaric aciduria type 1 (GA1; OMIM #231670) is a rare autosomal recessive-inherited neurometabolic disorder caused by the deficiency of glutaryl-CoA dehydrogenase (GCDH), which is encoded by the GCDH gene. It results in the accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC). These metabolites are considered to damage the striatum through an excitotoxic mechanism. The treatments of GA1 known to date are metabolic maintenance treatment based on a low-lysine diet and emergency treatment during acute illness. However, treatment after the onset of neurological symptoms has limited effectiveness and is associated with poor outcomes, and the effect of treatment and disease course after treatment are not good. After the implementation of newborn screening, the incidence of acute encephalopathic crisis fell to 10%–20% with early diagnosis, preventative dietary management, and aggressive medical intervention during acute episodes. Recently, several cohort studies have been published on the natural course and treatment of GA1 patients. This mini review will cover the clinical symptoms, natural history, and treatment of GA1 through a literature review.

Keywords: Glutaric aciduria type 1, Glutaryl-CoA dehydrogenase, Metabolic disease, Organic aciduria

Introduction

Glutaric aciduria type 1 (GA1; OMIM #231670) is a rare, autosomal-recessive inherited neurometabolic disorder of L-lysine, L-hydroxylysine and L-tryptophan metabolism result from deficiency of glutaryl-CoA dehydrogenase (GCDH)[1]. It is caused by pathologic mutation of *GCDH* gene, which is located on chromosome 19p13.2, resulting in accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC) in body tissues, particularly within the brain[2]. The accumulation of these metabolites was thought to influence in the development of the striatal damage via an excitotoxic mechanism[3]. More than 200 disease-causing mutations in the *GCDH* gene have been identified[4]. The estimated prevalence of GA1 reported from 1:125,000 in worldwide to 1:250 newborns in genetic high-risk populations[5,6]. GA1 has two different phenotypes; infantile-onset type is characterized by striatal injury and progressive movement disorder, which often precipitated by an acute encephalopathic crisis within the first three years of life or late-onset type is the first three years of life and has insidious presentation and variety of neurologic symptoms including chronic headaches, peripheral neuropathy, white matter abnormalities and subependymal nodules[1,2,7-9]. Historically, before execution of newborn screening (NBS) program for GA1, 80–90% of affected patients presented with acute encephalopathic crises with severe striatal injury result in progressive and irreversible brain damage[10]. The implementation of NBS changed the incidence of acute encephalopathic crises fell to 10–20% by early diagnosis, aggressive medical intervention during acute episode, and low lysine diet[11-14]. This dietary-based therapy remains to most important treatment of patients with GA1[10,15], This minireview of GA1 will be covered in the clinical manifestations, natural histories and treatments.

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Clinical Characteristics and Natural History

To date, several literatures of patient cohort with GA1 reported the descriptions of the clinical phenotype and natural history of GA1. Traditionally, the subtypes of untreated GA1 ranges from the more common form (infantile-onset type) to the less common form (later-onset type after age 6 years)[2].

Kurkina et al. reported 51 patients confirmed with GA1 from 49 Russian families, and Russia is a country that has not yet implemented NBS for GA1[6]. The clinical manifestations began before the age of 24 months in 76.6% of all patients and in 8.5% manifested at 3-5 years of age. Macrocephaly was observed in 74.5% of all paitents and principal clinical symptoms was generalized dystonia, epileptic seizure as complications of acute encephalopathic crisis. It has been predicted that patients with regression of motor development and delay in cognitive development will have an aggressive course of the disease. Despite the management, these patients still have serious neurological sequelae. Before NBS program for GA1 was administered, the clinical manifestations and natural course of most GA1 patients were similarly reported[5,16-20].

After the introduction of NBS, asymptomatic GA1 patients were diagnosed immediately after birth, and there were many changes in the clinical pattern and natural course of the patients[11]. Recently, Strauss et al. reported on the treatment and outcome of 168 patients, the largest of the GA1 cohorts reported to date, for 30 years[13]. These patients were classified into three cohorts according to the timing of diagnosis and treatment strategy. Cohort 1 was diagnosed when asymptomatic by NBS, and consisted of 60 patients treated with lysine free, arginine-enriched metabolic formula, L-carnitine supplement, emergency iv infusion of dextrose, saline, L-carnitine during acute illness immediately after diagnosis, and cohort 2 was also diagnosed at asymptomatic period by NBS, however these 57 patients treated with a protein restriction diet, instead of metabolic formula. Cohort 3 were 51 patients who were diagnosed after symptoms appeared before NBS and did not receive preventative therapies. The incidence of striatal degeneration was significantly low in Cohorts 1 (7%) compared with Cohort 2 and 3 (47%, and 90%, respectively) ($p<.0001$). Mhanni et al. also reported that acute encephalopathic crisis decreased from 90% to 60% in 20 years after the introduction of NBS as a result of analyzing a cohort of 39 patients with GA1 from 1980 to 2020[21]. Boy et al. recently reported meta-analysis results involving 647 GA1 patients reported in 15 publications[22]. In the NBS group (n=261 patients), 74.7% of patients remained asymptomatic, while 25.3% of patients developed a complex movement disorder with acute (59.0% of symptomatic patients), insidious (34.8% of symptomatic patients) or unreported onset type (6.1%). In contrast, most targeted metabolic study (TMS) group (n=386 patients), most patients (90.4%) were symptomatic at time of diagnosis with acute (69.9%), insidious (22.6%), or unreported onset type (7.5%). NBS group showed a significantly higher proportion of normal motor development (mean: 84.4%; 95% CI: 72.2–94.2%) than TMS group (mean: 6.0%; 95% CI: 0.0–18.8; QM [df=1]=61.57; $p<0.0001$). Patients not following guideline for low-lysine diet and carnitine supplementation showed a trend for increased relative risk (log risk ratio) for insidious onset disease compared with patients with recommended dietary treatment (QM [df=14]=29.14; $p=0.058$; og RR: 0.61; 95% CI: 0.02–1.25). Based on these studies, NBS programs for GA1 have an overall positive neurological outcome of the GA1 patients, but their success principally depends on the quality of therapy.

Cohort studies on small-scale GA1 patients have been published in Japan[17] and China[19,23], but domestic GA1 patients have not been published except for case reports[24-26].

Treatments

Management of GA1 includes metabolic maintenance treatment based on a low lysine diet and emergency treatment during acute illness. The guidelines for the diagnosis and treatment of GA1 were first published in 2007[27], and revised guidelines were released in 2011[10] and 2017[15].

Treatments of GA1 are divided into metabolic maintenance treatment including dietary therapy, supplemental pharmacotherapy, and emergency treatment during acute encephalopathic crisis. Treatment should be performed even during diagnostic work-up due to suspected GA1, and a multidisciplinary team approach at a specialized center is required for effective treatment. In the case of diagnosis after the occurrence of neurological symptoms, the effect and disease course of treatment are not good.

Dietary Treatment Combined with Carnitine Supplementation

The purpose of dietary treatment for GA1 aims to reduce the intake of lysine, the most associated amino acid for neurotoxicity, while maintaining sufficient intake of essential amino acids and energy substrates. A lysine-free tryptophan reduced amino acid mixture (AAM) containing minerals, trace elements, and vitamins should be given to all GA1 patients until age 6 years. After

age 6 years, dietary treatment should follow an age-adapted protocol based on safe levels for protein intake. Dietary liberalization should be accompanied by regular advice from specialized nutritionists and clinicians. Effectiveness of dietary treatment critically depends on adequate provision of information and education to patients and their caregivers[7]. L-carnitine supplementation is recommended to reduce striatal injury risk and mortality rates in patients with GA1. Usually, starting with L-carnitine 100 mg/kg per day, the dose was adjusted to keep the plasma free L-carnitine concentration in the normal range.

Emergency Treatment

It is important to apply the emergency treatment protocols, if patients are at risk for catabolism caused by febrile illness, febrile reactions to vaccination, or perioperative period. This protocol is based on the basic treatment principles for intoxication type metabolic diseases as follows: (1) prevent or reverse a catabolic state by administering a high-energy intake; (2) reduce production of neurotoxic GA and 3-OH-GA by restriction of protein for 24–48 hours; (3) carnitine supplementation; (4) balance electrolytes and pH status via IV fluids.

Conclusion

We still do not know the exact mechanism of neuropathogenesis of GA1, but it seems to clear that neonatal diagnosis and early preventative managements including dietary therapies and emergency treatments preventing acute encephalopathic crisis are safe and effective for normal growth and development and preventing striatal injury in patients with GA1. In order to understand and properly manage this metabolic disorder that can cause severe neurological deficit, further studies are needed on natural history, long-term outcomes, treatment monitoring strategy, genotype-phenotype correlation, and reliable detection method of low-risk patients.

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