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김 수 진

Glutaric Aciduria Type I: The Newborn Screening Program Changes the Outcomes of the Disease

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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. Infantile-onset GA1 is the most common form characterized by striatal injury and progressive movement disorder, and it is often triggered by an acute encephalopathic crisis within the first three years of life. Once this crisis occurs, there is a high likelihood for ineffective or limited conventional interventions, neurological disorders, or even death. Therefore, early diagnosis and immediate preventive management, such as dietary therapy, is essential. In the past decades, newborn screening (NBS) by tandem mass spectrometry for GA1 has been largely introduced in many countries including Korea, and it has led to improvements in the neurological outcomes of patients with GA1. In this review, the clinical symptoms, natural histories, and outcomes before and after the introduction of NBS in patients are discussed.

Key words: Glutaric aciduria type 1, Newborn screening, Glutaryl-CoA dehydrogenase, Inherited metabolic disease

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 caused by a deficiency of glutaryl-CoA dehydrogenase (GCDH)[1]. In 1975, Goodman et al. first described this neurodegenerative disorder, characterized by opisthotonos, dystonia, and progressive choreoathetosis, at the start of early infancy[2]. GCDH convertts glutaryl-CoA to glutaconyl-CoA, and its insufficiency or absence results in the accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC) in body fluids and tissues[1,3]. Accumulation of these metabolites impedes the development of striatal damage via an excitotoxic mechanism[4]. GCDH is encoded by the GCDH gene, which is located on chromosome 19p13.2, and to date, more than 200 disease-causing mutations in the *GCDH* gene have been identified[5]. The estimated prevalence of GA1 is reported to be from 1:100,000

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to 1:210,000 in live newborn worldwide[6,7]. Traditionally, GA1 has exhibited two different clinical spectra: the infantile-onset type and the late-onset type. The former is characterized by striatal injury and progressive movement disorder, which is often exacerbated by the occurrence of an acute encephalopathic crisis within the first three years of age. Meanwhile, the latter is defined by the onset of clinical symptoms after six years of age and is seen in about 10-20% of patients. Moreover, clinical manifestations of this type are also insidious as it is subtle, vague, and may not be as apparent since its symptoms include a variety of common neurological issues, such as chronic headaches, peripheral neuropathy, and other white matter abnormalities[8-10].

Recently, in many countries, the GA1 screening method for measuring the concentration of C5DC in dried blood spots was included in the newborn screening (NBS) program, and this has reduced the incidence of acute encephalopathic crises and has improved the neurological outcomes of patients through early diagnosis, aggressive medical intervention during acute episodes, and preventive low-lysine diet during childhood[3,11-13]. Therefore, clinical manifestations, natural histories, and outcomes before and after NBS introduction are discussed in this review.

Clinical characteristics of GA1

To date, the clinical phenotype and natural history of GA1 have been reported in various GA1 patient cohorts. Both the subtypes of GA1 (infantile-onset and late-onset) vary in occurrence especially in untreated patients. Similarly, the clinical phenotype can also vary even among family members with the same genotype[6,8], wherein the occurrence of a particular GA1 subtype depends on the age of the patient in which the acute encephalopathic crisis has started. This may be between three months to three years for infantile-onset GA1, or after six years for late-onset GA1. Specifically, acute encephalopathic crises are caused by an acute bilateral striatal damage followed by progressive dyskinesia[14,15] and are triggered by fasting, post-vaccination febrile episodes, acute illnesses with fever, or any stressful condition associated with anesthesia and surgical procedures. In such cases, there is a high likelihood for ineffective or limited conventional interventions and treatment, neurological disorders, or even death.

Kolker et al.[16] reported 279 patients (160 males and 119 females) with GA1 most of whom were diagnosed after clinical manifestations had ensued. In symptomatic patients, the most predominant symptom was encephalopathic crisis (78%), such that 95% had experienced it in the first 24 months of life. This was followed by macrocephaly (74%), which was particularly found at birth and without any other characteristic signs prior the onset of the encephalopathy crisis. According to the Kaplan-Meier survival analysis, approximately 50% of the symptomatic patients after the onset of the crisis die by the age of 25- aspiration pneumonia being the most common cause of death. In a cohort study of 51 patients in Russia[7], conducted prior to NBS for GA1, clinical symptoms started in 76.6% of the patients under two years old, while it appeared in 8.5% of patients between three to five years old. Meanwhile, macrocephaly was observed in 74.5% of the patients in which general dystonia and seizures resulting from acute encephalopathy crisis were the main clinical manifestations observed. Moreover, severe neurological sequelae still occurred in patients despite provisions of nutritional

support. Prior to the implementation of the NBS program for GA1, the clinical symptoms and natural histories of GA1 patients were reported to be largely similar[6,14,17–20].

The late–onset type, as it is an acute crisis that starts between the ages of three and six years of age, has been reported to account for 10–20% of all symptomatic patients[1,16]. Brain magnetic resonance imaging (MRI) scans showed that patients had suffered from less severe movement disorders and less extensive lesions than those with infantile–onset–type GA1[15]. Meanwhile, in patients with symptoms of chronic headache, epilepsy, tremor, gait disturbance, and dementia that had manifested at the start of six to 71 years[10,21,22], the brain MRI scans had showed various abnormalities such as subependymal nodules, frontotemporal hypoplasia, and abnormal white matter signals. However, owing to its early diagnosis and preventive nutritional management (i.e., low–lysine diet), the late–onset GA1 type has now been increasingly diagnosed easily with the introduction and expansion of NBS.

Introduction of Newborn screening and changing of the natural history and the outcomes of GA1

Most newborns or infants with GA1 do not have specific symptoms aside from macrocephaly. However, the onset of acute encephalopathic crisis can be its first actual manifestation and in such cases, treatment efficacy or even prognosis may be difficult thereafter[12]. Hence, aside from the early diagnosis prior to its onset, low–lysine diets with carnitine supplementation and emergency treatment, are essential in patients with GA1[12,23]. Although GA1 is already currently included in NBS in Korea and many other countries[3,24–26], these findings provide adequate justifications on its inclusion in the NBS. Further, the medical costs are also highly cost–effective when tandem mass spectrometry is used, as shown in several studies [27–29].

The inception and expansion of NBS has enabled earlier diagnosis for asymptomatic GA1 patients soon after birth, and this has changed the clinical characteristics. In a large cohort study of the treatment and outcomes of patients before and after NBS introduction, three cohorts from 168 patients with GA1 over 30 years old[13] were categorized according to diagnostic time and treatment strategy. The first cohort (n=60) was diagnosed as asymptomatic by NBS (n=60), and immediately treated with a lysine–free, arginine–enriched metabolic formula combined with L–carnitine supplement after diagnosis, including emergency supportive management during acute illness (i.e., saline infusion with dextrose and carnitine). Cohort 2 (n=57) was also diagnosed by NBS; the patients were treated with a protein–restricted diet instead of a metabolic formula in the asymptomatic period after diagnosis. Cohort 3 (n=51) was diagnosed after the onset of neurological symptoms before NBS was administered and did not receive preventative diet therapies. Here, it was found that the incidence of striatal degeneration was significantly lower in cohort 1 (7%) than in cohorts 2 and 3 (47% and 90%, respectively) ($p<0.0001$). Similarly, in another long–term cohort study in Manitoba from 1980 to 2020 involving 39 patients with GA1, it was also reported that in this period, acute encephalopathic crisis had decreased from 90% to 60%[30]. Recently, Boy et al.[31] had demonstrated that NBS for GA1 has an overall positive effect on the neurological outcome of patients based on a meta–analysis that were reported in 15 publications

involving 647 GA1 patients. In the NBS group (n=261), 74.7% of the patients remained asymptomatic, while 25.3% of the patients developed a complex movement disorder. In symptomatic patients, 59% exhibited infantile onset, 34.8% insidious onset, 6.1% had an unreported onset. In contrast, 90.4% of the patients diagnosed in a targeted metabolic study (n=386) were symptomatic at the time of diagnosis. In the NBS group, a higher percentage of the patients showed normal motor development than in the TMS group (mean: 84.4% vs. mean: 6.0%; p<0.0001). Patients who did not follow the guidelines for the low-lysine diet and carnitine supplementation showed an increased relative risk for movement disorders compared with patients who followed the recommended dietary treatment (p=0.058; log RR: 0.61). These findings reveal that in addition to early diagnosis by NBS, appropriate and high-quality treatment are also important for the prognosis of GA1.

Pitfalls of newborn screening for GA1

False-positive or false-negative results, including the development of metabolic disorders, are unavoidable pitfalls of NBS for GA1. Specifically, false-positive findings may generate anxiety among parents, which may in turn, place them at risk for parent-child dysfunction owing to increased stress levels[32]. Meanwhile, false-negative findings may worsen the prognosis of early-diagnosed patients especially those asymptomatic, since preventive diet therapy must be religiously administered. Spenger et al.[33] reported that four missed cases by NBS resulting in false-negative NBS results had been due to these diagnostic errors arising from the variety of newborn characteristics. Considering that the main cause of GA1 is the deficiency in special enzymes such as GCDH, the two subtypes were needed to be further classified according to the residual enzyme activity or levels of toxic metabolites because of the different metabolic profiles of high and low excretors: high excretion (with complete lack of GCDH activity or GA≥100 mmol/GA/mol creatine) and low excretion (with up to 30% residual GCDH activity or GA<100 mmol/GA/mol creatine)[16,34]. Patients with the former may experience more diagnostic challenges, but they can have normal C5DC levels even with carnitine supplementation. Since the clinical course and prognosis of the two subtypes are deemed similar, which makes it controversial, adjusting the cutoff and introducing various ratios to increase the sensitivity and specificity of NBS to GA-1 may be crucial[33,35-37]. Additionally, genetic testing in patients with clinically suspected or ambiguous biochemical profiles is also important to confirm the diagnosis.

Conclusion

Early diagnosis and immediate preventive management such as dietary therapies, are important for patients with GA1 to prevent striatal injuries especially during an acute encephalopathic crisis and encourage their normal growth and development. With the inclusion of GA1 in the NBS over the past few decades, the outcomes of patients with GA1 have been manageable. However, improving the long-term prognosis of asymptomatic patients is still necessary to enable more accurate results. This can be achieved using high-quality treatment based on a multidisciplinary approach.

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