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Original Article

Experiences during newborn screening for glutaric aciduria type 1: Diagnosis, treatment, genotype, phenotype, and outcomes

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Abstract

Background: Glutaric aciduria type 1 (GA-1) is an organic acidemia with potentially severe neurological sequelae. In Taiwan, newborn screening (NBS) for GA-1 began in 2001, but large-scale reporting is lacking. This study describes Taiwan's largest newborn screening population to date.
Methods: Between 2001 and 2015, 1,490,636 newborns were screened for GA-1. Confirmatory examinations included the carnitine loading test. Confirmed patients were treated with a low lysine diet, carnitine, and high-energy intake during illness. Clinical, laboratory, and neuroimaging data were analyzed.
Results: Fourteen newborns were diagnosed with GA-1 (incidence: 1/106,474). C5DC concentration was clearly increased after carnitine loading in the affected newborns, but not in false-positive newborns ($p = 0.004$), indicating that this test is useful as an adjuvant diagnostic method. Eleven patients followed in our hospital were enrolled, namely nine NBS patients and two patients diagnosed clinically. IVS10-2A>C was the most common mutation. Two novel mutations (T36fs and N291K) were identified. Pendular nystagmus was found in two pediatric GA-1 patients. The corresponding pathology was optic atrophy in one patient, but remained undetermined in the other patient. The frequency of encephalopathic crisis decreased substantially following NBS. Among patients diagnosed by NBS, cognitive functioning was better among patients with good compliance than patients with poor compliance ($p = 0.03$). Abnormalities were detected by brain MRI including diffusion-weighted imaging and apparent diffusion coefficient maps; these affected various brain regions at different stages of the disease. Basal ganglion injuries occurred after an encephalopathic crisis. White matter disease was prevalent among older patients, either with or without an encephalopathic crisis.
Conclusion: Early diagnosis by newborn screening followed by full compliance with treatment guidelines is important to a good outcome.

Keywords: glutaric aciduria type 1; newborn screening; nystagmus; optic atrophy; Taiwan

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Glutaric aciduria type 1 (GA-1) is an autosomal recessive organic aciduria caused by glutaryl-CoA dehydrogenase (GCDH) deficiency.[1] This results in impaired metabolism of L-lysine, L-hydroxylysine and L-tryptophan, leading to an accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC). GA and 3-OH-GA are putatively neurotoxic.[2] More than 200 disease-causing mutations in the GCDH gene (chromosome 19p13.2) have been identified.[3,4]

Without treatment, around 90% of patients will suffer from an acute encephalopathic crisis between 3 to 36 months of age. The crisis is often precipitated by infection, vaccination, and/or surgery.[5] The neurological sequela is striatal injury, which manifests as dystonia and axial hypotonia.[6,7] Encephalopathic crises are associated with high morbidity and mortality.[5,8] Some patients develop neurological impairment but have no documented encephalopathic crisis; these are classified as insidious-onset.[9,10] Macrocephaly is a common presentation during infancy, but is frequently overlooked. Due to absence of characteristic features before an encephalopathic crisis, early diagnosis is difficult. Consequently, newborn screening for GA-1 has been established. Treatment for GA-1 consists of a low lysine diet, carnitine, and high-energy intake during illness.[11] Early diagnosis and rigorous treatment have lowered the frequency of encephalopathic crises.[5,7,12] Despite early treatment, neurodevelopmental deficits are commonly detected.[13]

In Taiwan, newborn screening for GA-I started in 2001 and has been mandated since 2006; however there have been only a few small-scale reports describing GA-1 in Taiwan.[14−17] We describe our experience with Taiwan's largest newborn screening population. This included eleven patients diagnosed with GA-1 (nine by newborn screening and two clinically). We have compared their outcomes.

2. Methods

2.1. Newborn screening for GA-1

Between January 2001 and October 2015, 1,490,636 newborns were screened for GA-1 using tandem mass spectrometry at the Taipei Institute of Pathology (TIP) and the Chinese Foundation of Health (CFH), two national newborn screening centers in Taiwan. Glutarylcarnitine (C5DC) concentration was measured. The borderline cut-off value for C5DC was $\geq$0.4 μM at the TIP, and $\geq$0.3 μM at the CFH. The positive cut-off values were >0.8 μM at the TIP, and $\geq$0.6 μM at the CFH. If the screened value was equal to or greater than the positive cut-off value, the newborn was referred for confirmatory diagnosis immediately. If the screening value was between the borderline cut-off value and the positive cut-off value, a second sampling was performed. If the second value was still abnormal, the newborn was referred for confirmatory diagnosis.

2.2. Confirmatory diagnosis

Urine organic acid and plasma amino acid analyses were performed. It has been reported that missed cases of GA-1 are possible due to secondary carnitine depletion.[18,19] To avoid false-negative C5DC results on repeated samples, we developed the carnitine loading test.[20] Carnitine (100 mg/kg/day) was given orally for 3 days. Dry blood spots were obtained before and 2 hours after the test. Mutation analysis was performed when urinary GA and 3-OH-GA were found or when the C5DC concentration was more than 0.3 μM after the carnitine loading test.

2.3. Patient management

Treatment was started immediately after diagnosis. The maintenance treatment consisted of carnitine and a low lysine diet supplemented with GA-1 special formula (Glutarex-1, Abbott Nutrition, Ltd., Columbus, Ohio, USA or GA1 Anamix Infant, SHS International, Ltd., Liverpool, Merseyside, UK). Recent studies demonstrated that arginine supplementation lowered cerebral GA and 3-OH-GA concentrations in a mouse model and could improve the GA-1 patient outcome, therefore arginine has been prescribed since 2012.[21−23] Parents were instructed regarding emergency treatment. During intercurrent illness, catabolism needs to be prevented promptly by providing a high-energy intake. Patients were seen at our clinic every three months. Non-contrast magnetic resonance imaging (MRI) including T1-weighted and T2-weighted images, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) maps were obtained at diagnosis and when new neurological symptoms presented.

Standard deviation scores for weight and height were calculated using the World Health Organization growth charts. Neurological outcomes were evaluated using cognitive functioning and disability scores as proposed by Kyllerman et al.[8] All children with GA-I who had undergone follow-up in our hospital since October 2002 were included. This study was approved by the institutional review board of the Taipei Veterans General Hospital, Taipei, Taiwan, ROC.

2.4. Statistics

Mann-Whitney U test, Kruskal-Wallis test, and Dunn's multiple comparison test were used. Statistical significance was identified when $p < 0.05$. Calculations were performed using GraphPad Prism, Version 6.0c (GraphPad Software, CA, USA).

3. Results

3.1. Newborn screening

Among the 1,490,636 newborns screened, 14 newborns were confirmed to have GA-1. The incidence of GA-1 in this

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