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Case Report

Reversible brain atrophy in glutaric aciduria type 1

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Abstract

Glutaric aciduria type 1 (GA1) is a rare metabolic disorder caused by a deficiency of glutaryl-CoA dehydrogenase. The typical clinical onset features an acute encephalopathic crisis developed in early childhood, causing irreversible striatal injury. Recently, tandem mass spectrometry of spots of dried blood has allowed pre-symptomatic detection of GA1 in newborns. Early treatment can prevent irreversible neurological injury. We report the case of a girl with GA1 who exhibited a characteristic reversible change upon brain magnetic resonance imaging (MRI). She was diagnosed with GA1 as a newborn. She commenced dietary carnitine and her intake of lysine and tryptophan were reduced at the age of 4 weeks. After treatment commenced, her mean glutarylcarnitine level was lower than that in the previous reports. The plasma lysine and tryptophan levels were maintained below the normal ranges. At 4 months, brain MRI revealed a widened operculum with dilatation of the subarachnoid spaces surrounding the atrophic bilateral frontotemporal lobes; this is typical of GA1 patients. However, at 17 months, MRI revealed that the atrophic lesion had disappeared and she subsequently underwent normal maturation. She has never suffered a metabolic decompensation episode. At 26 months, her development and brain MRI were normal. The present reversible brain atrophy in a patient with GA1 indicates that early dietary modifications with a lower level of glutarylcarnitine and administration of carnitine can lead to normal development.

Keywords: Glutaric aciduria type 1; Glutaric acid; Reversible brain atrophy

1. Introduction

Glutaric aciduria type 1 (GA1) is a rare autosomal recessive metabolic disorder caused by a deficiency in glutaryl-CoA dehydrogenase (GCDH); this enzyme plays roles in the breakdown of lysine, hydroxylysine, and tryptophan to acetyl-CoA. The frequency of GA1 is approximately 1 in 100,000 newborns on the basis of North American, Australian and German neonatal screening programs [1]. Although more than 150 *GCDH* mutations are known, no correlation between any mutation and the biochemical phenotype or genotype has yet been established [2,3]. Accumulation of toxic metabolites, including glutaric acid (GA), 3-hydroxyglutaric acid (3-OHGA), and glutarylcarnitine, causes neurological damage. These metabolites begin accumulating in utero [4]. The typical clinical course of GA1 features an episode of acute metabolic encephalopathy [5], which causes irreversible striatal injury.

Recently, the tandem mass spectrometric measurement of glutarylcarnitine levels in dried blood spots has allowed pre-symptomatic detection of GA1 in newborns, allowing treatment to be commenced early. The

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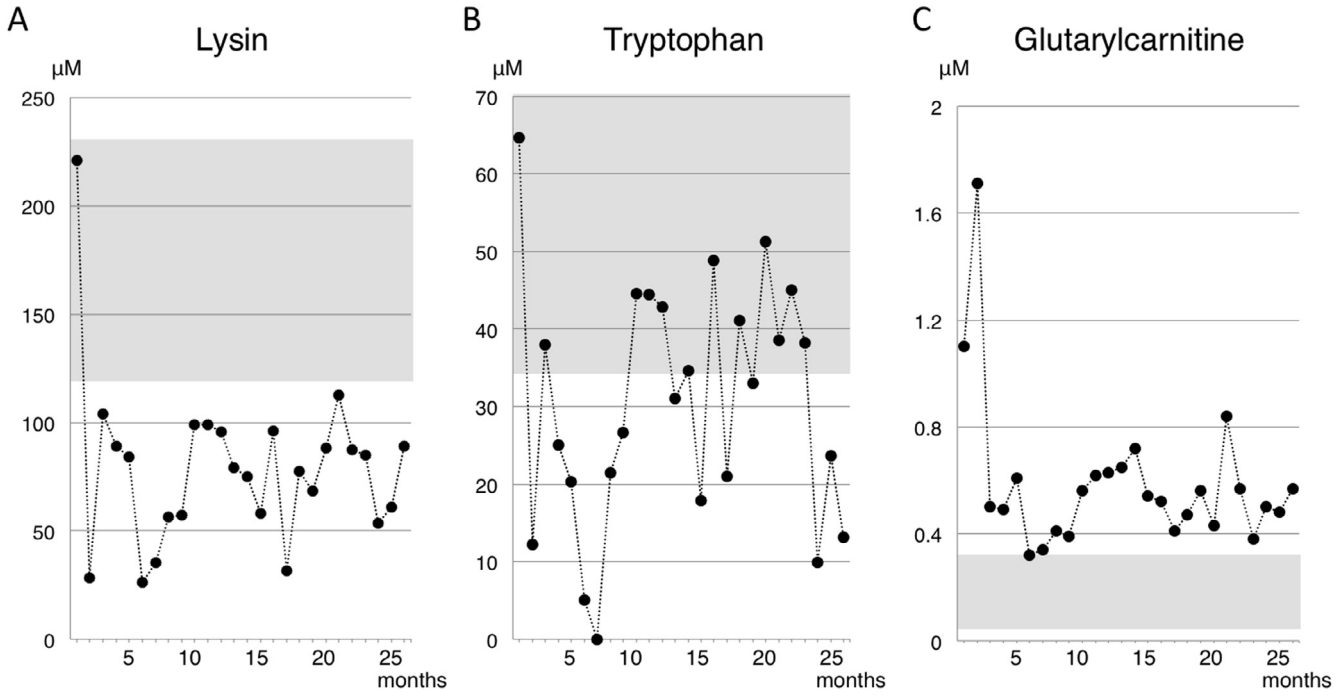

Fig. 1. Plasma amino acid and dried blood spot acylcarnitine profiles. Plasma lysine (A), tryptophan (B), glutarylcarnitine (C) levels. The normal range for the each plasma amino acid and glutarylcarnitine are indicated in gray.

frequency of acute encephalopathic crises is lower in such patients. Patients lacking encephalopathic crises commonly show alteration of the front temporal cerebrospinal fluid (CSF) spaces [6]. One report showed that abnormalities (including brain atrophy) in some patients without encephalopathic crises regressed or even disappeared with time [6]. However, the clinical courses of and biological data of GA1 patients with normalized brains have not been described. Herein, we herein present a GA1 case with magnetic resonance imaging (MRI) abnormalities, including widening of the anterior temporal and sylvian CSF spaces, which regressed over time. We also report on her clinical course and biochemical data.

2. Case report

2.1. Clinical course

A baby girl from non-consanguineous Japanese parents was born at 40 weeks of gestation after a normal pregnancy. Her birth weight was 3850 g (+1.9 standard deviation [SD]), her length was 53 cm (+1.9 SD), and her head circumference was 36.5 cm (+2.4 SD). She was diagnosed with GA1 by virtue of an abnormal glutarylcarnitine level and laboratory data. Oral administration of pharmaceutical L-carnitine commenced at the age of 4 weeks, combined with a reduction in lysine intake; lysine is quantitatively the most relevant amino acid precursor of neurotoxic GA and 3-OHGA. Good head control was evident at 4 months of age. At 8 months, she sat independently. She could walk alone by 14 months of age. At 26 months of age, her motor and mental development was normal. Her head circumference ranged from +2.4 SD to +1 SD and was 48.9 cm (+1.1 SD) at 26 months of age. Although she sometimes had colds and fevers, she never suffered from a metabolic decompensation episode, such as consciousness disturbance or a seizure associated with infection or fever. She exhibited no dystonia.

2.2. Laboratory data

Mass spectrometry of dried blood performed soon after birth revealed a high level of glutarylcarnitine (1.16 μM; cutoff, <0.25 μM). Urine organic acid analysis revealed large peaks of GA and 3-OHGA, suggesting a diagnosis of GA1. After dietary treatment commenced, her mean dried blood spot glutarylcarnitine level was 0.52 μM (range, 0.32–0.84 μM) (Fig. 1). Her plasma amino acid and dried blood spot acylcarnitine profiles were monitored monthly. Her plasma lysine (mean, 75.3 μM; range, 26.2–112.5 μM) and tryptophan (mean, 31.1 μM; range, 0–51.3 μM) levels were maintained at lower levels than the normal ranges (Fig. 1).

2.3. Genetic testing

Mutational analysis of the *GCDH* gene revealed compound heterozygosity for the known mutations c.416C>T (p.S139L) and c.1157G>A (p.R386G).