Biochemical and Clinical Findings in the First Two Cases of Glutaric Aciduria Type I in the Philippines

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ABSTRACT

We report the first two diagnosed cases of Glutaric Aciduria Type I (GA I) in the Philippines. The diagnosis was confirmed by urinary organic acid analysis by Gas Chromatography-Mass Spectrometry (GC-MS) which showed the characteristic metabolites for GA I. Review of their clinical features showed macrocephaly, developmental delay, seizures, dystonia and choreoathetotic posturing. Cranial CT scan findings were also compatible with previously reported cases. This paper emphasizes the usefulness of locally available biochemical tools in the diagnosis of inborn errors of metabolism as well as the importance of clinical recognition of these disorders.

Key Words: Glutaric Aciduria Type I, cerebral organic aciduria, urine organic acid analysis

Introduction

Glutaric aciduria type I (GA I) is a rare genetic metabolic disorder with a worldwide prevalence of approximately 1 in 60,000 to 1 in 100,000 individuals.[1,2] It is caused by the deficiency of the enzyme glutaryl CoA-dehydrogenase, which plays a major role in the metabolism of lysine, hydroxylysine, and tryptophan.[3,4] It is an autosomal recessive disorder which manifests with macrocephaly, fronto-temporal atrophy, encephalopathic crisis, striatal degeneration, and a severe dystonic-dyskinetic movement disorder.[5] Presence of 3-hydroxyglutaric acid, along with increased glutaric acid, detectable through urine organic acid analysis is diagnostic of this condition.[4,5] GA I can be identified by newborn screening programs by the detection of increased glutaryl carnitine (C5DC).[4]

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Here we report the first two cases of GA I in the Philippines diagnosed through urine organic acid analysis performed at our institute.

Clinical Reports

Patient 1

This 2-year-old female was born to a non-consanguineous Filipino couple. She was delivered at term after a pregnancy complicated by UTI and subchorionic bleeding. Macrocephaly was noted at birth and there was early onset developmental delay. Dystonic posturing was noted at 7 months of age. A brain CT scan performed at 9 months of age showed fronto-temporo-parietal atrophy and bilateral arachnoid cysts. Her EEG was normal. Physical examination revealed that her weight was below the 5th percentile for age and head circumference was +>2SD for age. She had frontal bossing but no other dysmorphic features. Neurologic examination demonstrated spasticity of her extremities with dystonic posturing of the upper extremities, left more than the right. The remainder of the physical examination was normal.

Patient 2

This 9-month-old male, born to a non-consanguineous couple, was delivered by cesarean section at term after a pregnancy complicated by bleeding during the first trimester. His birth weight was 2.3 kg. Frequent vomiting and slow weight gain were observed during the first 3 months of life. During this time, macrocephaly was noted. At 6 months, he had dystonic posturing of both upper extremities. He had an early onset developmental delay. Physical examination showed that his length and weight were at the 10th-25th percentiles for age and the head circumference was 50 cm, which was >+2SD for age. He had frontal bossing but had no other dysmorphic features. Neurologic examination showed dystonic and choreoathetotic movements with normal muscle tone and reflexes. A brain MRI scan revealed chronic subdural hemorrhage in the left cerebral and right anterior frontal convexities.

Method: Urine organic acid analysis

Urine sample was obtained using random collection and creatinine was determined for each sample. Extraction of organic acids from the urine was achieved by acidification, salt saturation, and ethyl acetate addition. Heptadecanoic acid served as the internal standard. The dried organic extract was derivatized using Regieil BSTFA + 1% trimethylchlorosilane. A final 20 nmol creatinine per μL of derivatized extract was then injected for analysis using Shimadzu GC-MS QP5050A.[6]

Biochemical Findings

Chromatographic profiles for Patient 1 and Patient 2 are shown in Figures 1 and 2, respectively.

The results for Patient 1 revealed grossly increased glutarate, slightly increased 3-hydroxyglutarate, and trace glutaconate which were highly indicative of GA I.

There was also a slight increase of adipate and trace 3-hydroxyisovalerate which suggested that the patient had mild ketosis at the time of sample collection.

In Patient 2, there was grossly increased glutarate,

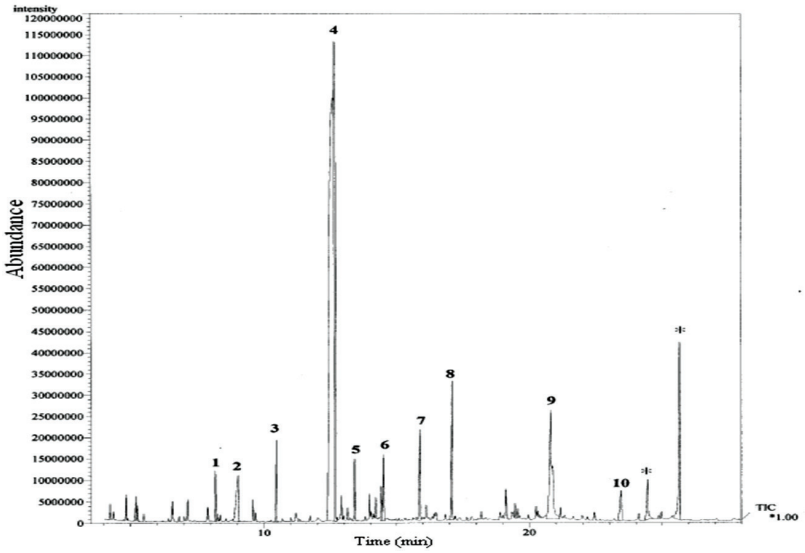

Figure 1. Total ion chromatogram of urinary organic acid metabolites of Patient 1. Peaks identified were (1) 3-hydroxyisovalerate, (2) urea, (3) succinate, (4) glutarate, (5) glutaconate, (6) adipate, (7) 3-hydroxyglutarate, (8) 4-hydroxyphenylacetate, (9) hippurate, (10) phenobarbital; *heptadecanoate (internal standard).

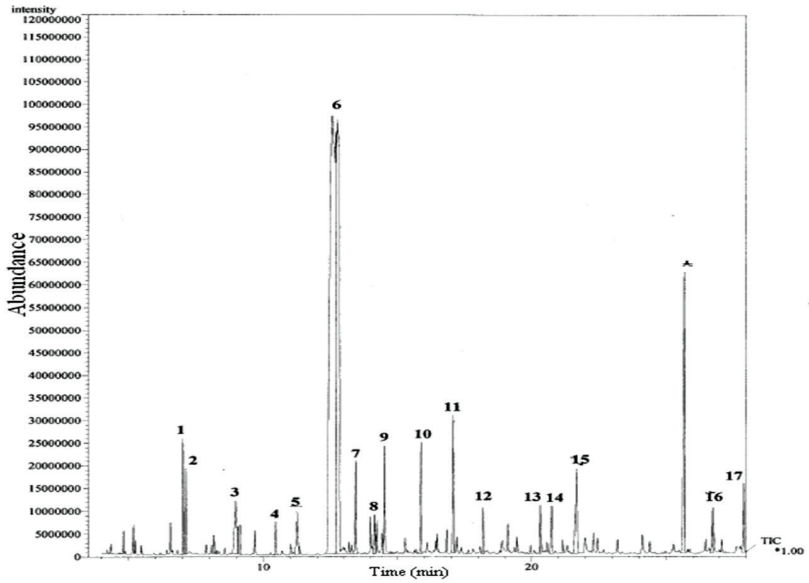

Figure 2. Total ion chromatogram of urinary organic acid metabolites of Patient 2. Peaks identified were (1) cresol, (2) 3-hydroxybutyrate, (3) urea, (4) succinate, (5) fumarate, (6) glutarate, (7) glutaconate, (8) metabolite of 2-ketoglutarate, (9) adipate, (10) 3-hydroxyglutarate, (11) 4-hydroxyphenylacetate, (12) suberate, (13) citrate, (14) hippurate, (15) 2-octenyl succinate, (16) 8-hydroxyoctenyl succinate, (17) osa-tca-1,2,9-non-enetricarboxylate; *heptadecanoate (internal standard).

slightly increased 3-hydroxyglutarate, and slightly increased glutaconate which were all highly indicative of GA I. Slightly increased adipate and trace suberate were also noted which suggested mild ketosis.

Discussion and Conclusion

The clinical manifestations of both patients were compatible with GA I.[3,4,5,7]

The diagnoses were confirmed by urine organic acid analysis which showed significant excretion of characteristic metabolites in GA I. The presence of markers for ketosis may indicate that both patients were in a catabolic state at the time of sample collection. The use of the GC-MS technique has been so far the most important technique in the diagnosis of organic acidopathies due to high sensitivity of organic acid metabolite detection at a short span of time. Availability of this test in the local setting is truly valuable and vital for the diagnosis and hence, management of rare diseases such as this.

GA I can be detected through newborn screening by tandem mass spectrometry. There is now clear evidence that presymptomatic diagnosis and management to avoid catabolism is effective in most cases, with good clinical outcome.[1,8] It is recommended that in the future, this technology be used to aid the early detection and appropriate management of the disorder, thus preventing the severe neurologic complications and physical debilitation from the disease.

Acknowledgments

We would like to express our gratitude to Dr. Ignacio Rivera, Dr. April Grace Berboso, and Dr. Mary Ann Abacan for contributing to the patients' clinical information.

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