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Case Report

Glutaric Acidemia Type-1: A Metabolic Challenge

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ABSTRACT

Glutaric Acidemia Type-1 (GA-1) is characterized by glutaryl-CoA dehydrogenase (GCDH) impairment. This enzyme deficit causes harmful metabolites, particularly glutaric acid, to accumulate in affected persons' tissues and fluids. We report a case series of four patients in our study with complaints of macrocephaly, poor head holding, and gross developmental delay. On the biochemical analysis, they had elevated levels of GA in urine organic acid level which confirmed the presence of GA type-1.

Keywords: Glutaric Acidemia type-1; Inherited Metabolic disorders; GCDH genes

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INTRODUCTION

Glutaric Acidemia Type-1 is an autosomal recessive cerebral organic acid metabolism disorder of L-tryptophan, L-hydroxylysine, and L-lysine developed due to the deficiency of glutaryl-CoA dehydrogenase (GCDH, EC 1.3.8.6). It occurs due to the mutation of the glutaryl-CoA dehydrogenase (*GCDH*) gene present on chromosome 19p13.2.[1,2] It leads to the accumulations of 3-Hydroxyglutaric acid, Glutaric acid, and Glutaconic acid. Without any therapy, more than 80% of children affected by this disease develop striatal degeneration under the age of two years.[3] The clinical symptoms include the abrupt development of hypotonia, encephalopathy, and macrocephaly, which often occurs before the age of 18 months.[4] Therapy consists of a low Lysine diet to decrease the production of Glutaric acid and Carnitine supplements to reduce Glutaric acid.[5]

METHODOLOGY

This case series data was collected in the Armed Forces Institute of Pathology, Rawalpindi from 2020 to 2022 on the patients who have GA-1 which was suspected based on history, clinical symptoms, and typical neuroimaging findings. The confirmation involved analyzing urine organic acids using the gas chromatography-mass spectrometry (GC-MS) and examining plasma amino acids through ion exchange chromatography. After receiving approval from the institutional review board, the laboratory, clinical, and neuroimaging findings were collected and placed into a proforma.

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Case-1: A 10-months-old male infant, first born to a consanguineous marriage presented in emergency with complaints of fever and 3 episodes of fits for the last 2 days. The child had an uneventful history before 4 months of age and was born at full term of gestation by normal delivery. After 2-3 febrile episodes the child lost his ability to hold his neck and there was a gross developmental delay with refusal to feed. He developed hypotonia and septicemia-like illness. CT examination showed that he had dilated lateral, 3rd, and 4th ventricles and moderate brain atrophy. Plasma amino acids analysis showed negative results. But the urine organic test shows an elevated level of Glutaric acid (concentration 7629 umol/L), at the retention time (RT) of 9.920 minutes as shown in Figure, suggesting Glutaric Academia type-1. He was prescribed to take carnitine and Riboflavin and a low-lysine diet.

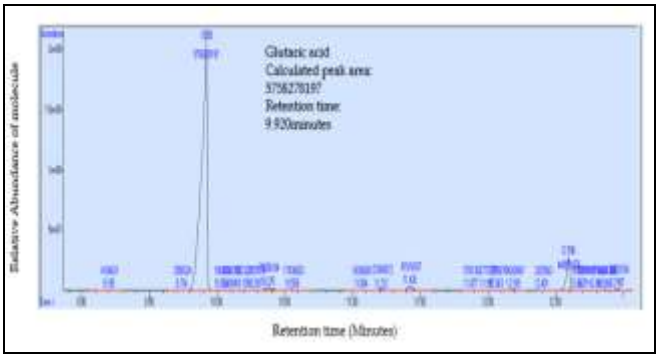

Figure: Urine Organic Acid Chromatogram with its Mass Spectrum Analyzed by the Gas Chromatography-Mass Spectrometry (GC-MS) showing a Peak of Glutaric Acid at 9.920min with Peak Area 5758278197

Case-2: An 18-month-old male patient born of consanguineous marriage was presented with

gross developmental delay, having a history of fever, vomiting, loose motion, failure to thrive, poor sucking/feeding, seizures/fits, septicaemia-like illness, hematuria, and mental retardation. Bio-chemical analysis shows that he had anemia, edema, dehydration, and dysmorphic features. On the examination, he was diagnosed with CNS hypotonia. Investigation showed deranged electrolytes, metabolic acidosis, mildly raised ammonia levels, and urine for ketones positive. The urine organic acid test shows the elevated level of glutaric acid (conc. 72.7 umol/L).

Case-3: An 8-month-old male baby presented with a rapid increase in head size, and poor motor and mental response. An MRI of the brain showed expansive CSF spaces along with underdeveloped temporal lobes, frontal and temporal shrinkage, widening of the Sylvian fissures with exposed opercula, and significant deep white matter underneath the cortex, indicating a likelihood of glutaric acidemia type-1. He had a history of fever, loose motion, hypotonia, and 2 episodes of seizures/fits for the last 6 days. Confirmation was done by an organic acid analysis of urine using the gas chromatography-mass spectrometry which shows a markedly elevated level of the glutaric acid. Treatment was done by using carnitine and Riboflavin supplementation and a protein-restricted diet. After a follow-up of 2-months he could sit with support and his head size remained static.

Case-4: The infant, a 5-month-old boy, results from marriage between blood relatives. He has been notably irritable and unwilling to take oral feeds for the past month. Upon examination of the central nervous system (CNS), there were no signs of papilledema or retinal hemorrhages. Additionally, the infant displayed low muscle tone and responsive reflexes in the feet. Organic acid tests showed the elevated level of glutaric acid (concentration 5365 umol/L) was suggestive of glutaric academia type-1. He was prescribed to take carnitine and Riboflavin supplementation.

The demographic, clinical, and biochemical findings of these patients are shown in the table showing the raised level of glutaric acid.

DISCUSSION

Glutaric aciduria type-1 (GA1) occurred due to the decreased level of the glutaryl-co-enzyme A (CoA) dehydrogenase (GCDH) enzyme encoded by the GCDH gene.[6] The global incidence of GA-1 is expected to be 1/100,000 live neonates.[6,7] Changes in the GCDH gene, found on chromosome 19p13.2 in humans and comprising 12 exons, resulting in the accumulation of glutaric acid (GS) and 3-hydroxyglutarate (3-OHGA) in the brain, resulting in nervous system impairments.[8]

We diagnosed 4 cases of GA type-1 based on urine organic acid level and plasma amino acid level, all presenting in childhood age. The main complaint was macrocephaly, seizures, poor head holding, gross developmental delay, fever, and hypotonia. A similar case is of an 8-month-old male patient who has a history of convulsions, altered sensorium, dystonic posturing, fever, and loss of motor and mental milestones (Sanju *et al*).[9] On the MRI examination he showed frontotemporal atrophy and basal ganglionic changes. On the biochemical analysis, he showed a normal level of plasma amino acid level but a high level of GA in the urine organic acid test which confirmed the presence of GA type-1. Similar symptoms were present in our 3rd case that had wide CSF spaces with the temporal lobe hypoplasia, frontotemporal atrophy, dilatation of Sylvain fissures with the open opercula, and deep subcortical white matter on the MRI investigation, and elevated level of GA in urine organic acid level test. Treatment of these patients was done by using Carnitine and Riboflavin supplementation and low Lysine diet. The patients were followed for a long period of time after giving medications which showed better results for the patient.

Conflict of Interest: None.
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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MUM & MB: Data acquisition, data analysis, critical review, approval of the final version to be published.

MQAK & NA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Table: Demographic, Clinical, and Biochemical Investigation of Cases

Gender	Age at diagnosis (Months)	Poor head holding	Consanguinity	Large head	Seizures	CT/MRI frontotemporal atrophy	Gross developmental delay
Male	10	+	-	+	+	+	+
Male	18	-	-	+	+	+	+
Male	8	+	+	+	+	+	+
Male	5	-	-	+	-	+	+

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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