CASE REPORT

Glutaric aciduria type 1 — importance of early diagnosis and treatment

Bushra Afroze,[1] Zabedah Mohammad Yunus[2]

Abstract

Glutaric aciduria type 1 is a rare inherited organic academia. Untreated patients characteristically develop dystonia secondary to striatal injury during early childhood, which results in high morbidity and mortality. In patients diagnosed during neonatal period, striatal injury can be prevented by metabolic treatment including low lysine diet, carnitine supplementation and aggressive emergency treatment during acute episode of inter current illnesses. However, after the onset of neurological damage initiation of treatment is generally not effective. Therefore; glutaric aciduria type 1 is included in newborn screening panel for inherited metabolic diseases in many countries.

We describe two children in a family with glutaric aciduria type 1 and their different long term outcomes. The first child was diagnosed late leading to severe neurological damage. The second child was diagnosed in the neonatal period as a result of selective high-risk screening and was treated appropriately giving a normal growth.

Keywords: Glutaric aciduria type I, emergency treatment, Pakistani children.

Introduction

Glutaric aciduria type 1 (GA-1) is an autosomal recessive disorder caused by deficiency of glutaryl-CoA dehydrogenase, which is the key mitochondrial enzyme involved in the final degradation of lysine, L-hydroxylysine and L-tryphtophan. If untreated, 90% of patients between 3-36 months of age suffer regression and severe dystonic-dyskinetic disorder.[1] Cognitive functions are relatively spared. Life expectancy is greatly reduced in symptomatic patients with movement disorder (MD).[2] Before the onset of an encephalopathic crisis, presentation of affected children is non-specific with macrocephaly being the most characteristic feature.[1]

Biochemically, GA-1 is characterized by marked increase of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA) in urine, plasma and cerebrospinal fluid which is detected by gas chromatography/mass spectrometry (GC/MS).[3] Detection of glutarylcarnitine (C5DC) by electrospray-ionization tandem mass spectrometry is used for newborn screening of GA-1.[4]

Heinger et al[5] have shown that maintenance treatment with low lysine diet and carnitine supplementation along with emergency treatment during inter-current illness according to the established guidelines,[6] prevents acute encephalopathic crisis and striatal damage.

We present two siblings with GA-1 having different outcomes, emphasizing the importance of early diagnosis and adherence to proper treatment. Elder child was diagnosed after encephalopathic crisis and suffers severe MD. While the younger child was diagnosed as the result of selective high-risk screening in the first week of life and treated promptly and is growing normally.

Case Report

Patient 1

A twelve month old girl was seen at the metabolic clinic for loss of motor milestones noted at 6 months of age. She was the second child of first-cousin parents who was born after a full-term, uneventful pregnancy. Her birth weight and length were at 50th centile and OFC was at 90th centile. The parents reported normal development till 6 months of age when sudden loss of milestones were noted following upper respiratory tract infection.

At twelve months she weighed 8.7kg (between 10th & 25th centile), her length was 74cm(at 50th centile) whereas her OFC was 49cm (>97th centile). She was also noted to have oro-facial and limb dystonia with truncal hypotonia. The parents brought in an MRI of the brain, which was done as part of evaluation of her loss of milestones. It showed significant fronto-temporal atrophy with open Sylvian fissure, delayed myelination and hyperintense signals in globus pallidus bilaterally (Figure). Widening of the Sylvian fissures, mesencephalic cistern, and enlarged pretemporal subarachnoid spaces are cardinal MRI features of GA-1.[7] Based on the clinical presentation and MRI findings, GA-1 was suspected and urine organic acid analysis was

[1]Department of Paediatrics & Child Health, The Aga Khan University Hospital, Karachi, Pakistan, [2]Institute Medical Research, Kuala Lumpur.
Correspondence: Bushra Afroze. Email: bushra.afroze@aku.edu

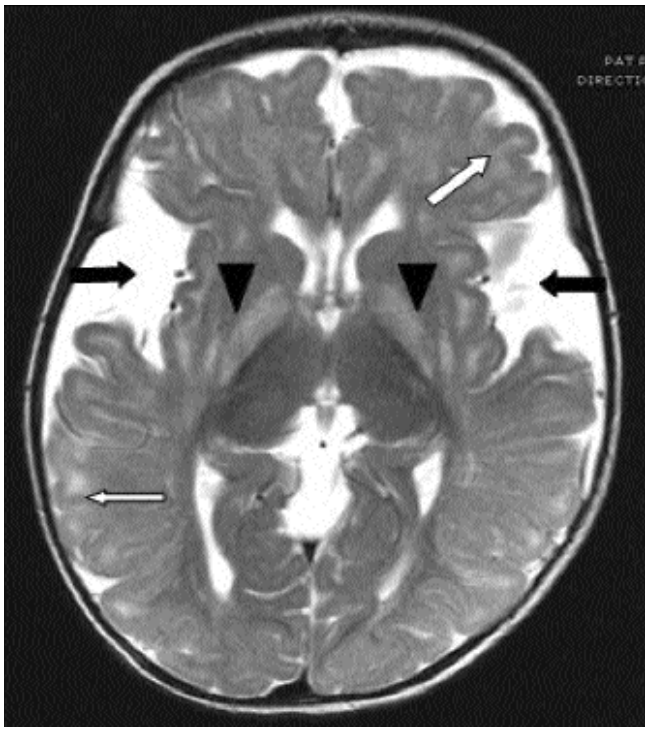

Figure: MRI brain T2-weighted image of patient 1. Black arrows showing open sylvian fissure secondary to fronto-temporal atrophy, black arrow heads showing hyperintense signals in globus pallidus, white arrows showing delayed myelination.

is relatively settled on oral Baclofen.

Patient 2

This was the brother of patient 1, who was born after a full-term, normal pregnancy. His birth weight was 3.6kg (at 50th centile), length was 50cm (at 50th centile) and OFC was 38.7cm (at 90th centile). Prominent veins over both the temporal regions were also noted after birth. High-risk selective screening for GA-1 was undertaken on day three of life via urine organic acid analysis, which showed large peak of GA and 3-OH-GA confirming diagnosis of GA-1.

The baby was treated with lysine free amino acid mixture and 100mg/kg of oral carnitine in two divided doses. He was allowed calculated amount of lysine according to age from natural protein. Parents were educated about emergency treatment at home as well as need of early hospitalization in case of trivial childhood illness. Emergency home treatment plan based on the guidelines for management of GA-1 was given to parents (Table).

At present he is 3 years 6 months old, weighs 15kg(on 50th centile), his height is 100cm(on 50th centile) and OFC is 51cm. He has normal development for his age. He is attending pre-school and is able to sing baby rhymes, identifies colours and shapes, fills colours in pictures, is toilet-trained, is able to ride a tricycle and speaks in sentences. He needed six hospitalizations after his birth for childhood illnesses like diarrhoea and upper respiratory tract infections. During hospitalization he was treated based on the guidelines for management of GA-1 (Table).

Table: Emergency treatment plan at home and hospital.

1. Cessation of natural protein intake for 24 to a maximum of 48 hours. Gradually increase natural protein intake over next 48-72 hours.
2. If patient is tolerating orally then continue lysine-free amino acid mixture.
3. Double dose of oral L-carnitine in 200mg/kg/day
4. Body temperature >38.5oC(101oF) to be treated with antipyretic like paracetamol or ibuprofen.
5. To provide adequate calories.

Home Treatment			Hospital Treatment	
Age (years)	Maltodextran (%)	Volume (ml per day)	Age(years)	Intravenous Glucose (gm/kg/day)
0.5	10	150ml/kg	0 -1	12 - 15
0.5 -1	12	120/kg	1 -3	10 -12
1 -2	15	100/kg	3 - 6	8 -10
2 -6	20	1200- 1500	6 -10	6 - 8
6 -10	20	1500 2000	>10	
>10	25	2000- 2500		

done, which showed large peak of GA and 3-OH-GA thus confirming the diagnosis of GA-1. Limitation of dietary treatment after striatal damage was discussed with the parents and they opted for low-protein diet and oral L-carnitine without lysine-free amino acid mixture.

At present she is 5 years old has no neck holding, is unable to sit and cannot speak any intelligent word. Her dystonia

Discussion

The estimated prevalence of GA-1 is 1 in 100,000

newborns[8] but varies considerably in different countries. It is one of the cerebral organic acidaemia, which lacks general metabolic derangements like hypoglycaemia, metabolic acidosis or hyperammonaemia seen in inherited metabolic disorders presenting with metabolic decompensation. Therefore; patient 2 was not screened for these metabolic derangements but was directly looked for GA and 3-OH-GA in urine. Positive outcome with use of maintenance and emergency treatment has placed GA-1 in treatable group of inherited metabolic disorders thus is included in the disease panel of expanded newborn screening in many countries. Treatment guidelines for GA-1 were recently revised.[9]

In Pakistan, neither the incidence of GA-1 is known nor the national newborn screening for inherited metabolic disorder exists. Thus children are often diagnosed after the encephalopathy crisis has occurred. Early clinical diagnosis is hampered by the lack of characteristic signs and symptoms except macrocephaly, which is seen in 75% of patients during infancy.[10] Macrocephaly was present in both patients described here.

Timely diagnosis before the neurological damage has occurred is important for two reasons; firstly timely treatment prevents irreversible neurological impairment, secondly after the neurological damage has occurred then the value of metabolic treatment is unclear.[6] Patient 1 was diagnosed after suffering from encephalopathic crisis therefore she was treated with low protein diet without lysine free amino acid mixture along with oral L-carnitine.

Patient 1 provided an opportunity for high-risk screening for her younger brother (patient 2), who was diagnosed in first week of life and treated promptly resulting in avoidance of the catastrophic event seen in patient 1. At present, in the absence of newborn screening in Pakistan, high-risk screening and cascade screening involving relatives of index patient to identify asymptomatic patients and carriers can help in achieving favourable outcome. Through this case report, we have demonstrated that even in our current resource-constrained health care system we can achieve similar favourable outcome in GA-1 like in countries with much better health care facilities.

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