ORIGINAL RESEARCH PAPER

Neurology

"CEREBRAL PALSY MIMIC OF A 5YEAR OLD GIRL CHILD"

KEY WORDS:

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ABSTRACT

Summary: Glutaric aciduria type I (GA I) is an autosomal recessive disorder caused by deficiency of Glutaryl CoA dehydrogenase, a mitochondrial matrix enzyme involved in the degradation of lysine, hydroxyl lysine and trypophan[1] resulting in accumulation of glutaric acid,3-hydroxy glutaric acid in central nervous system.The estimated prevalence of GA-I is approximately 1 in 1,00,000 live births.[2] The classic symptom of glutaric aciduria type I (GAI) is irreversible focal striatal necrosis during an acute illness, most often between the ages of 3 and 18 months termed as "Encephalopathic crisis" results in dystonic-dyskinetic disorder.

BACKGROUND:

GA-I is an inborn error of metabolism of lysine, hydroxyl lysine and tryptophan due to deficiency of Glutaryl CoA dehydrogenase resulting in accumulation of glutaric acid, 3-OH GA causing neuronal damage and striatal neuronal loss. Clinical features include macrocephaly, Irreversible disabling dystonia, choreoathetosis, vomiting, seizures with shortened life expectancy.Systemic manifestations typical of many other organic acidemias, such as pronounced metabolic ketoacidosis, hypoglycemia, and hyperammonemia, generally do not occur.

Casereport:

A 5 year old girl child born of second degree consanguineous parentage with history of birth asphyxia, global developmental delay and history of epileptic encephalopathy at age of 13months with macrocephaly Figure-1 and dysmorphic facies (hypertelorism and depressed nasal bridge) with chronic progressive spastic paraparesis with dystonic posturing of right lowerlimb Figure-2 , striatal toe and varus deformity of foot with brisk tendon reflexes and bilateral extensor response of plantars without any sensory, cranial nerve, cerebellar or autonomic involvement.

Routine Biochemical investigations are normal.MR imaging of brain revealed Symmetrical T2 and FLAIR hyperintensities in bilateral dentate nuclei and bilateral basal ganglia with expansion of CSF spaces anterior to bilateral temporal poles and sylvian fissures (Bat-wing appearance Figure-3A,B) suggestive of GA-I.

Plasma Glutamic acid levels are in normal range 78µmol/L. Urine sample was sent for Gas chromatography and mass spectrometry,which revealed remarkable increase in glutarate and 3-hydroxyglutarate Figure-4 and was finally diagnosed as Glutaric aciduria type –I. She was treated with Protein restricted diet with low lysine and carnitine supplementation. Dystonia was managed by anticholinergics, benzodiazepines and baclofen.

DISCUSSION:

The list of Cerebral palsy mimics are numerous which include GA-I, Holocarboxylase synthetase deficiency, Arginase deficiency, Pyruvate dehydrogenase deficiency, Zellweger syndrome, Adrenoleukodystrophy, Infantile refsum disease, Niemann-pick disease[3]. GA-I has autosomal recessive inheritance with heterogenous mutations on GCD gene located on chromosome 19p causing Glutaryl CoA dehydrogenase deficiency. The main pathogenesis include Encephalopathic crisis leading to accumulation of toxic metabolites which mediate excitotoxicity through NMDA receptor leading to disabling dystonia, dyskinesia and shortenend life span.

Clinical features include Macrocephaly, acute neurological illness (mostly febrile illness) followed by a window of neurological susceptibility to striatal damage leading to irreversible dystonia, choreoathetosis, seizures and shortened life span.

The three "signature" MR imaging findings of classic GA-1[4]

(1) Macrocrania,
(2) Bilateral widened ("open") lateral cerebral or sylvian fissures (i.e., widened operculum) "Bat-wing" configuration
(3) Bilaterally symmetric basal ganglia lesions.

With urine organic acid analysis, 3-OH-glutaric acid is the diagnostic metabolite. In the classic patient, glutaric acid remains very elevated even when there is no catabolic state. Glutaric acid can be completely normal in some patients, but 3-OH-glutaric acid is always elevated. GA-1 produces carnitine deficiency and increases levels of C5 dicarboxylic (glutaryl) carnitine in urine and plasma.

Elevated Glutarylcarnitine in urine virtually diagnostic of this condition.Enzyme assay in cultured fibroblasts should be used for definitive confirmation of glutaric acidemia type 1.

Treatment options include Dietary protein restriction supplemented with lysine-free special formulas and carnitine (100 mg/kg/day) supplements. Growth and development monitoring is plasma amino acids to keep all amino acids in the normal range and lysine at or slightly below the normal range (60-90 micromolar conc.) Symptomatic management of seizures, dystonia and Choreoathetosis. Educating the parents about metabolic crisis is important.

CONCLUSION:

1. This case was mistaken for Spastic CP because of birth asphyxia and Glutaric aciduiria type-1 is a close mimic of CP, but Macrocephaly is a clue that it is not CP.
2. Non-febrile seizure with LOC for few days in this child would have resulted in striatal necrosis.
3. A widened sylvian fissures with striatal atrophy in MR Imaging of brain are diagnostic of this condition.
4. This neurometabolic disorder is a treatable condition to some extent with diet restriction and carnitine, just like cerebral palsy.

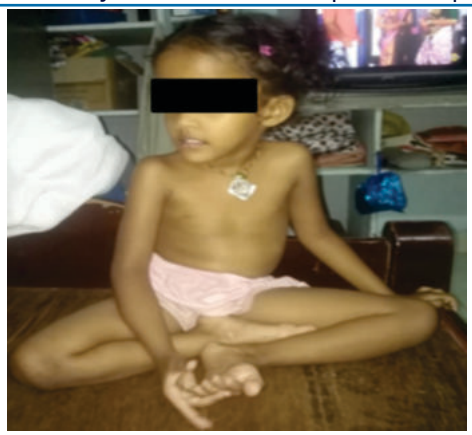

Figure-1:

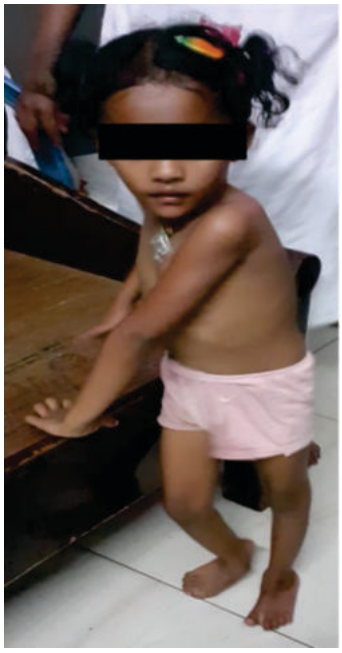

Figure-2:

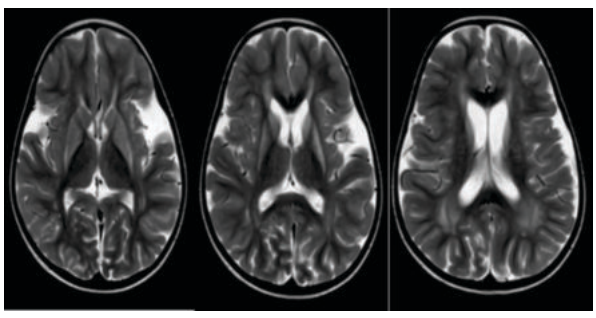

Figure-3:(A)

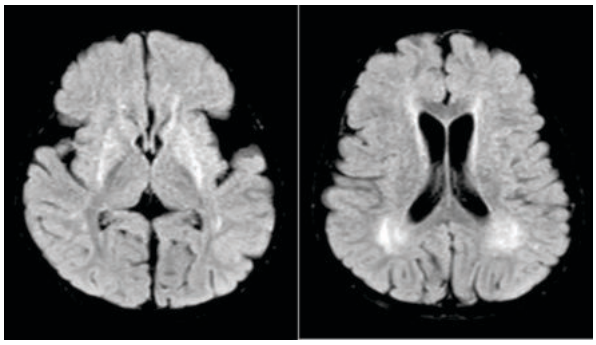

Figure-3:(B)

Figure-4:

Quantitative Report -Metabolic Profile: Values of Significant Markers –

Sr. No.	Compounds	Reference Value	Analysis Value	Magnification
1	Lactate	0.907	1775.977	1958.078
2	**Glutarate**	**0.013**	**4000.617**	**307739.800**
3	**3HG**	**0.017**	**480.113**	**28241.970**
4	2HG	0.158	300.259	1900.321
5	3HIV	0.336	499.815	1487.541
6	4HPL	0.084	163.130	1941.677

Note- The values are calculated as peak area ratio of metabolite peak area / creatinine peak area in a chromatogram.

REFERENCES:

1. HoffmanGF, Trefz FK, Barth PG, Böhles HJ, Biggemann B, Bremer HJ, *et al*. Glutaryl-coenzyme A dehydrogenase deficiency: A distinct encephalopathy. Pediatrics 1991;88:1194-203.
2. Fu Z, Wang M, Paschke R, Rao S, Frerman FE, Kim JJP.Crystal structures of human glutaryl-CoA dehydrogenase with and without an alternate substrate: Structural bases of dehydrogenation and decarboxylation reactions. Biochemistry 2004;43:9674-84.
3. Uptodate.com
4. Osborn's Brain Imaging,Pathology and Anatomy. Second edition chap 31 pg 1006