Clinical features and course of glutaric aciduria-Report of six cases

Sir,

Glutaric aciduria forms a rare group of metabolic diseases with treatment options if diagnosed early. Type 1 has a prevalence of about 1 per 100,000 and characterized by accumulation of 3-OH glutaric acid and presents with hypoglycemia, vomiting, sweaty feet, chorea and failure to thrive.[1] In Type 2 there is accumulation of 2-hydroxy glutaric acid and has a wide spectrum of presentation in clinico-demographic factors and associated with acidosis, hypoglycemia, coma, heart, liver, kidney, pancreas and skull involvement and a late form having a relatively benign course.[2-4] Type 3 glutaric aciduria is a single peroxisomal enzyme defect causing very long-chain fatty acid deficiency and has got an entirely different clinicoradiological presentation which includes adrenoleucodystrophy and adrenomyeloneuropathies.

Patients with Type 1 and Type 2 are treated with "Well way diet" consisting of low lysine and tryptophan.

Bread, wheat and wheat products with a daily allowance of 100-150 kcal/kg/day containing low protein with a calorific value of 100-115 kcal/kg/day; protein permitted is 1-1.25 g/kg/day, ready made preparations are available which can be used up to 350 mg/kg/day (max dose 8 g/day) containing l-carnitine, creatine, and glutamine:

L1 Glutaric aciduria showing A. Subdural effusion and B. Showing Frontotemporal atrophy with white matter changes

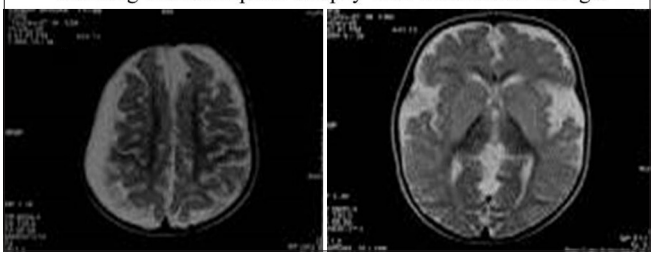

Figure 1: Open opercula, basal ganglia and white matter changes, sub-dural effusion and atrophy

L2 Glutaric aciduria – FLAIR images showing White matter and Caudate hyperintensities

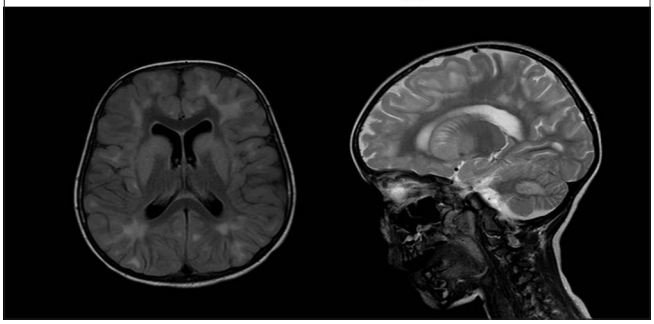

Figure 2: Periventricular white matter changes and caudate, putamen and dentate nucleus hyperintensities

Table 1: Demographic and clinical data

Diagnosis	Age	Gender	Consanguinity	Febrile seizures	Non-febrile seizures/type	Development	Movement disorders	Pyramidal signs	Head circumference
L1 (patient 1)	2 years	Male	Present	Present	Present/ GTCS	Global delay with acute encephalitis like presentation	Generalized dystonia and chorea	Absent	Normal
L1 (patient 2)	3 years	Male	Present	Absent	Present/ GTCS	Global delay	Nil	Absent	Normal
L2 (patient 3)	4 years	Female	Present	Present	Present/ focal motor	Normal	Nil	Absent	Normal
L2 (patient 4)	10 years	Male	Present	Absent	Present/ GTCS	Global delay	Ataxia	Absent	Megalencephaly HC-55.5cms
L2 (patient 5)	28 years	Female	Present	Absent	Present/ myoclonic	Cognitive delay	Ataxia and myoclonus	Present	Normal
L2 (patient 6)	40 years	Female	Present	Absent	Absent	Normal	Chorea	Present	Normal

GTCS: Generalized tonic clonic seizure

Table 2: Other system changes including dysmorphism

Diagnosis	Skeletal changes	Facial dysmorphism	Skin changes	Heart, kidney and liver involvement
L1 (patient 1)	Nil	Flat nose, low set ears, inverted upper lip	Nil	Hepatomegaly
L1 (patient 2)	Nil	Flat nose, high arched palate	Nil	Normal
L2 (patient 3)	Nil	Flat nose	Hyperextensible joints	Normal
L2 (patient 4)	Scoliosis, dolicocephaly, tilted pelvis, flat foot	Abnormal ears, high arched palate, flat nose	Café-au-lait spots, hyperextensible joints	Normal
L2 (patient 5)	Scoliosis	Nil	Nil	Normal
L2 (patient 6)	Nil	Nil	Nil	Normal

Table 3: Radiological features

Diagnosis	Subdural effusion	Open opercula/bat wing appearance	Cortical atrophy	White matter hyperintensity	Basal ganglia changes
L1 (patient 1)	Present	Present	Frontal, parietal and temporal	Present	Present
L1 (patient 2)	Present	Present	Frontal and temporal	Present	Present
L2 (patient 3)	Absent	Absent	Temporal lobe	Predominantly around frontal and occipital horn. T2 and FLAIR hyper and T1 hypointense signal changes.	Swollen appearance and signal changes present in caudate, putamen and dentate nucleus
L2 (patient 4)	Absent	Absent	Absent	Diffuse subcortical white matter changes including external capsule in T2 and FLAIR	Bilateral thalamic hypointensity, and dentate hyperintensity
L2 (patient 5)	Absent	Absent	Diffuse atrophy	Diffuse subcortical white matter changes including external capsule in T2 and FLAIR	Signal changes present in caudate, putamen and dentate nucleus
L2 (patient 6)	Absent	Absent	No atrophy	T1 and FLAIR white matter changes including U fibers	Basal ganglia signal changes present

Table 4: Metabolic parameters

Diagnosis	Blood sugars	Blood gases	Bicarbonate	Serum electrolytes	Serum ammonia	Urine for abnormal metabolites
L1 (patient 1)	Low	Normal	Normal	Normal	Normal	Normal
L1 (patient 2)	Normal	Normal	Normal	Normal	Normal	Normal
L2 (patient 3)	Normal	Normal	Normal	Normal	Mildly elevated	Normal
L2 (patient 4)	Normal	Normal	Normal	Normal	Normal	Normal
L2 (patient 5)	Normal	Normal	Normal	Normal	Normal	Normal
L2 (patient 6)	Normal	Normal	Normal	Normal	Normal	Normal

Table 5: Tandem mass spectrometry

Diagnosis	Aminoacid panel	Acylcarnitine panel
L1 (patient 1)	Normal	Free carnitine, acetyl carnitine and glutaryl carnitine elevated
L1 (patient 2)	Normal	Free carnitine, acetyl carnitine and glutaryl carnitine elevated
L2 (patient 3)	No abnormality detected	No abnormality detected
L2 (patient 4)	No abnormality detected	No abnormality detected
L2 (patient 5)	No abnormality detected	No abnormality detected
L2 (patient 6)	No abnormality detected	No abnormality detected

Table 6: Urine organic acid profile

Compounds	L1 (patient 1)	L1 (patient 2)	L2 (patient 3)	L2 (patient 4)	L2 (patient 5)	L2 (patient 6)
Oxalic-2	Not done	Not done	Insignificant elevation	1.8-fold elevated	Insignificant elevation	Insignificant elevation
Valproic acid (VPA)-1	Not done	Not done	Elevated (2-5-fold elevated)	Normal		
Isobutryl glycine-1	Not done	Not done	Insignificant elevation	Normal	Insignificant elevation	Insignificant elevation
2-Propyl, 3-OH, Pentanoic acid -2	Not done	Not done	Elevated (2-5-fold elevated)	Normal	Insignificant elevation	Insignificant elevation
Isovaleryl glycine-1	Not done	Not done	Insignificant elevation	Normal	Insignificant elevation	Insignificant elevation
Thiodiglycolic-2	Not done	Not done	Insignificant elevation	*3.8-fold elevated	Insignificant elevation	Insignificant elevation
2-Propyl-Hydroxyglutaric-2	Not done	Not done	Elevated (2-5-fold elevated)	Normal	Insignificant elevation	Insignificant elevation
Tiglylglycine-1	Not done	Not done	Insignificant elevation	Normal	Insignificant elevation	Insignificant elevation
2-OH glutaric -3	Not done	Not done	23.6-fold elevated	*34.8-fold elevated	Significantly elevated	Significantly elevated
3-OH-Phenylacetic-2	Not done	Not done	Insignificant elevation	Normal	Insignificant elevation	Insignificant elevation
4-OH-benzoic-2	Not done	Not done	Insignificant elevation	Normal	Insignificant elevation	Insignificant elevation
2-OH-adipic-3	Not done	Not done	Insignificant elevation	Normal	Insignificant elevation	Insignificant elevation

Patient 4-compounds 2, 4 and 7 elevations suggest valproate treatment

Table 7: Urine chromatography

Diagnosis	Internal control vs. case
L1 patient 1	Not done
L1 patient 2	Not done
L2 patient 3	Significantly elevated 2-OH glutaric acid (three times elevated)
	2-Ketoglutaric acid oxime (three times elevated)
	2-Deoxy tetronic acid (three times elevated)
	Succinic acid, thiodiglycolic acid, 2-propyl, 5-OH pentanoic acid (two times elevated)
L2 patient 4	Significantly elevated 2-OH glutaric acid (three times elevated)
L2 patient 5	Significantly elevated 2-OH glutaric acid (two times elevated)
L2 patient 6	Significantly elevated 2-OH glutaric acid (two times elevated)

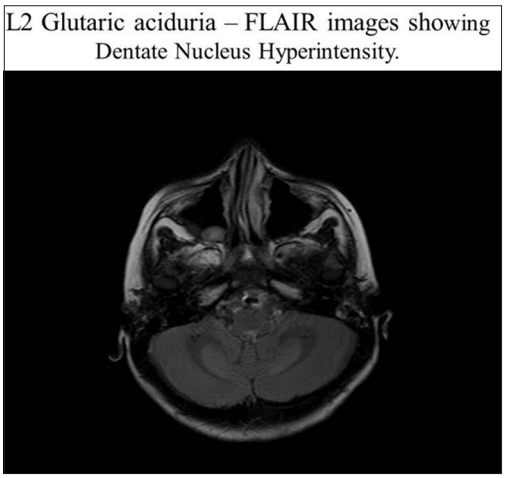

Figure 3: Dentate nucleus hyperintensities

100 mg/kg/day each along with riboflavin and alpha-lipoic acid: 10 mg/kg/day each, coenzyme Q10: 8.4 mg/kg/day, pantothenic acid: 5.6 mg/kg/day, alpha-linolenic acid: 150 mg/kg/day, complete pediatric vitamin: 1/2 tablet daily for infants, 1 tablet for young children. Home well-day consists of phenobarbital: 4-6 mg/kg-day titrated to therapeutic drug level and sick-day medications consist of extra dose with anti-inflammatory, antibiotic and anti-emetics. Type 2 glutaric aciduria is treated with prevention of infection, effective maintenance of glycemic levels, supplementation of riboflavin up to 400 mg/day, vitamin C and carnitine.[2] Effective measures are taken to control inflammation, infection, dehydration, electrolyte balance and glycemic control along with managing other system-related co-morbidities when there is encephalopathy. We

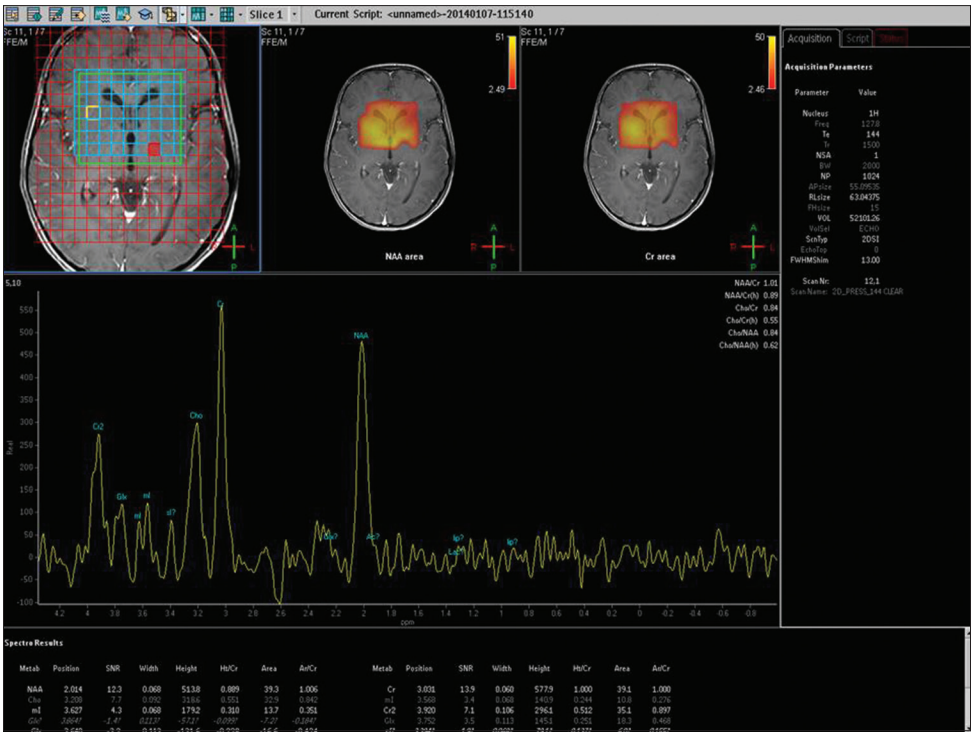

Figure 4: MRS showing small choline and no lactate peak in L2 glutaric aciduria

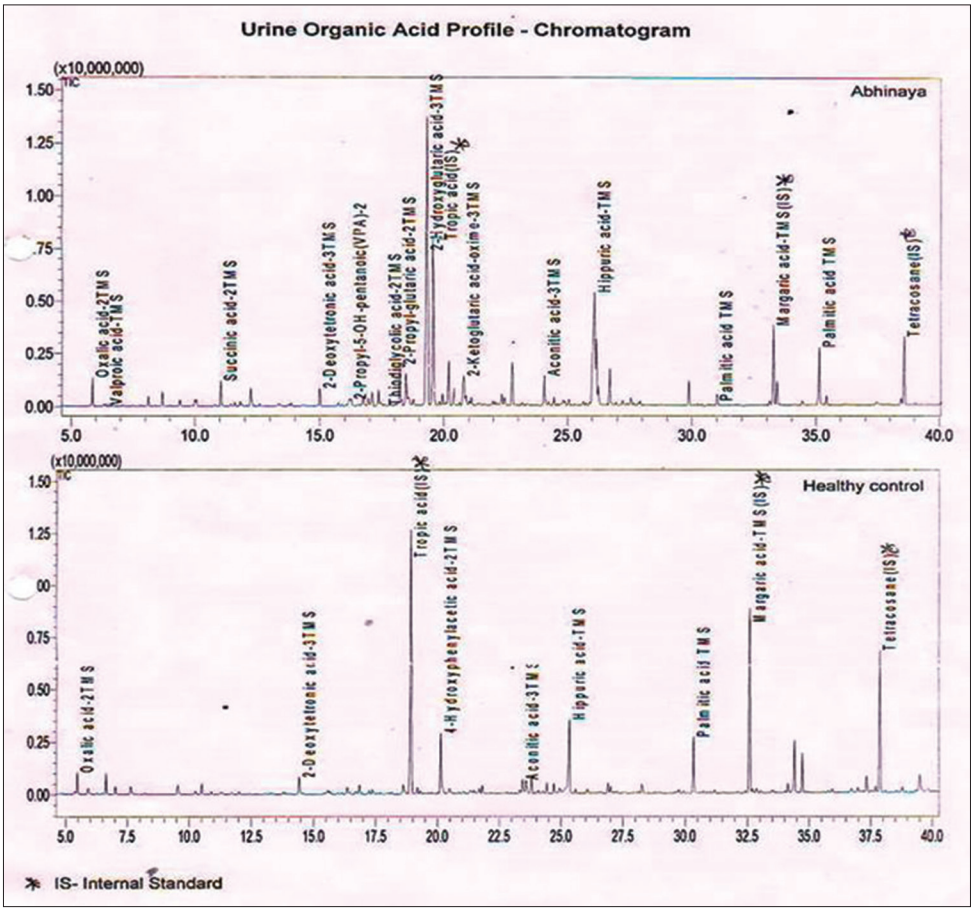

Figure 5: Urine chromatography showing 2-hydroxy glutaric acid peak

describe two cases of L1 and four cases of L2 followed up for 3-4 years with characteristic clinical features [Tables 1 and 2], radiological features [Table 3 and Figures 1-4], tandem mass spectroscopy, urine for organic aciduria and chromatography [Tables 4-7 and Figure 5]. The study reveals that L1 glutaric aciduria presents with early, more serious neurodevelopmental and systemic complications and invariably mistaken as infective encephalopathy. L2 can show normal development and late development of seizures and cognitive impairment.[5,6] Use of specific diet combined with disease-modifying and symptom-modifying treatment reduces morbidity greatly. They have unique radiological features, variable clinical features and are partly treatable. Therefore, a high degree of suspicion is important for diagnosis so that specific treatment can be initiated.

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Website: www.ruralneuropractice.com

DOI: 10.4103/0976-3147.150284