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Clinical Brief

Glutaric Aciduria Type I Associated with Learning Disability

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Abstract. The authors report a 7-year-8-months-old boy with glutaric aciduria type I who had associated dyslexia, dysgraphia and dyscalculia. The diagnosis of glutaric aciduria type I was confirmed on the basis of characteristic neuroimaging and biochemical findings. Axial T_1-weighted magnetic resonance imaging scan of the brain showed fronto-temporal atrophy, open opercula and bat-wing dilatation of the sylvian fissures. Axial T_2-weighted and FLAIR imaging showed hyperintense signal abnormality in both putamen and in the fronto-parietal deep white matter. Urinary aminoacidogram by thin layer chromatography revealed a generalized aminoaciduria. Urinary organic acid analysis by gas chromatography- mass spectroscopy revealed a marked excretion of glutaric acid. Psychoeducational testing was used to diagnose the learning disability. We postulate that the accumulation of glutaric acid and other metabolites was responsible for the child developing the associated learning disability. **[Indian J Pediatr 2004; 71 (10) : 1-3]** *E-mail: karandesunil@yahoo.com*

Key words : *Child; Dyscalculia; Dysgraphia; Dyslexia; Glutaric aciduria type I; Inborn error of metabolism.*

Glutaric aciduria type I (GA-I) is an autosomal recessive metabolic disorder of lysine and tryptophan metabolism caused by absence or markedly decreased activity of the mitochondrial enzyme glutaryl-coenzyme A dehydrogenase (GCDH). [1-3] This enzyme catalyses the dehydrogenation-decarboxylation of glutaric acid, an intermediary metabolite in the degradation pathway of lysine, hydroxyl-lysine and tryptophan.[1-3] Excessive accumulation of glutaric acid and other metabolites is believed to be responsible for the manifestations in this rare neurodegenerative metabolic disease. [3] The usual age of presentation for GA-I is 6 months to 2 years of life. Acute neuroregression or dystonia following an initial phase of normal or almost normal development, at times preceded by seizures, is a common mode of presentation.[1-3]

However, GA-I has also been reported to have protean manifestations.[2-4] A few patients present subacutely with motor delay in the first months of life followed by increasingly severe choreoathetosis and dystonia at a later age.[2-5] We describe such a patient with GA-I who had been referred to our Learning Disability (L.D.) Clinic for scholastic difficulties. Since 1996, the Government of Maharashtra has recognized the problems faced by school children with learning disability (dyslexia, dysgraphia, and dyscalculia) and offered them academic concessions, so that they can continue their schooling. Our L.D. Clinic is the only government-approved certification center in the state of Maharashtra for children with learning disability.[6]

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CASE REPORT

A 7-year-8 month-old boy, the first child born of a third degree consanguineous marriage, of Moslem extraction, was referred to our L.D. Clinic in September'2002 by his school headmistress for repeatedly making spelling mistakes, difficulty in writing sentences, poor handwriting, abnormal speech and being unable to cope up with his studies. He was studying in the III standard of an English medium school. His birth history was normal. His birth weight was 3 kg. At 9 months of age a doctor had noticed that the child had a large head, and a CT scan brain had been done. However, details of the clinical examination and investigations done at that time were not available. Also the CT scan was not traceable. The parents had not followed up with the treating pediatrician. However, the parents clearly remembered that the child's motor development was delayed. He had achieved head holding at 8 months, and was able to walk without support at 30 months of age, but with an unsteady gait. Till date the child had not achieved ability to run. His social milestones were apparently normal. However, he had delayed speech development. He had started speaking monosyllables at 42 months of age. The parents also gave history of noticing involuntary movements in their son since the last 18 months, which had commenced insidiously and then gradually increased in intensity. For the involuntary movements, they had consulted a

pediatrician and an MRI brain had been done in June'2002 which revealed features characteristic of GA-I (Figs. 1a, 1b and 1c). Axial T_1- weighted magnetic resonance imaging scan of the brain showed fronto-temporal atrophy, open opercula and bat-wing dilatation of the sylvian fissures (Fig. 1a). Axial T_2-weighted and FLAIR imaging showed hyperintense signal abnormality in both putamen and in the fronto-parietal deep white matter (Figs. 1b and 1c).

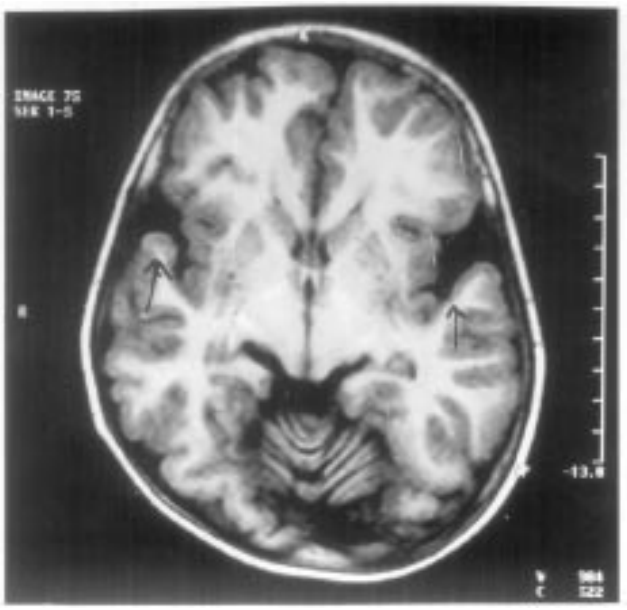

Fig. 1a. Axial T_1-weighted magnetic resonance imaging scan of the brain showing fronto-temporal atrophy, open opercula and bat-wing dilatation of the sylvian fissures.

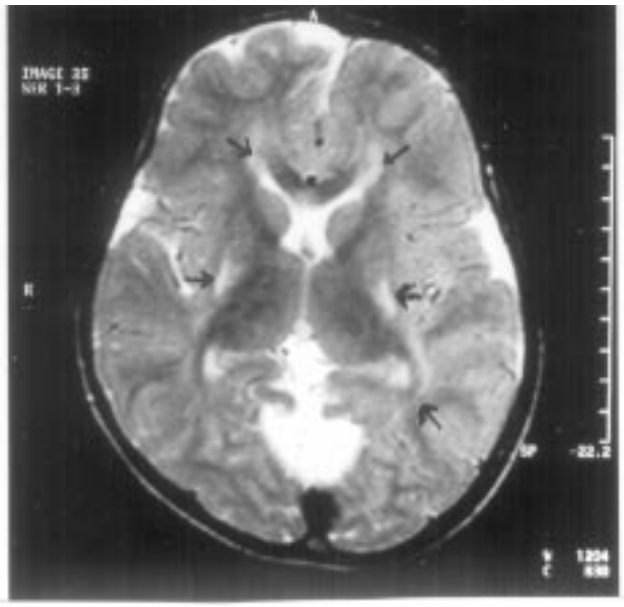

Fig. 1b. Axial T_2- weighted magnetic resonance imaging scan of the brain showing hyperintense signal abnormality in both putamen and in the fronto-parietal deep white matter.

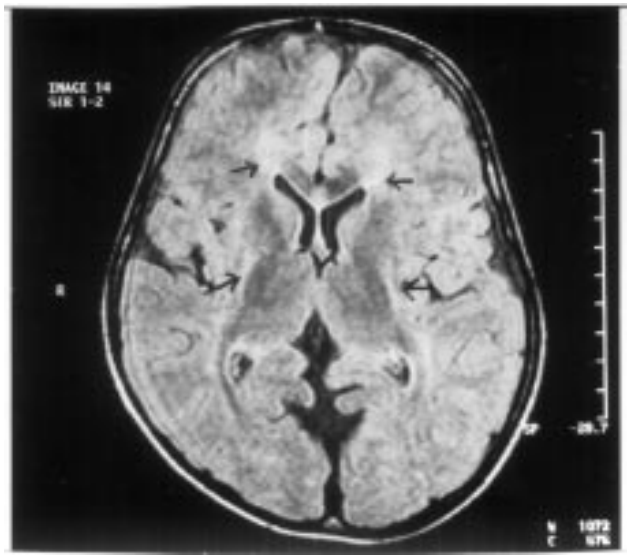

Fig. 1c. Axial FLAIR magnetic resonance imaging scan of the brain showing hyperintense signal abnormality in both putamen and in the fronto-parietal deep white matter.

The cerebral cortex, brain stem, cerebellum, and both caudate nuclei and thalami were normal. The child had no past history of seizures or altered sensorium.

On examination, the child was of average built and height. His vital parameters were normal. His head circumference was 53 cm (normal). On central nervous system examination, his higher functions were normal. His speech was slow, muffled and unclear. He had dystonia and choreoathetoid movements of the limbs with cogwheel rigidity. His deep tendon reflexes were brisk and he had bilateral ill sustained ankle clonus. Plantars were flexors. His gait was unsteady. Cranial nerve examination was normal. His vision and hearing testing were normal. Other systems examination was normal.

The child's arterial blood gas analysis was normal. Ketone bodies were absent in the urine. There was no hypoglycemia or hyperammonemia. The plasma aminoacidogram done by thin layer chromatography (TLC) method was normal. Urine aminoacidogram done by TLC method revealed a generalized aminoaciduria, with prominent spots of histidine, lysine, glycine, glutamic acid and alanine being detected. Urine organicacidogram by TLC showed a prominent spot for glutaric acid (Fig. 2).[7] Urine organic acid analysis by gas chromatography- mass spectroscopy (GC-MS) revealed a marked excretion of glutaric acid (Fig. 3a and 3b). The diagnosis of GA-I was confirmed on the basis of the characteristic MRI brain findings and biochemical studies. He was advised the recommended therapeutic regimen for GA-I consisting of a low lysine diet, with supplementation with riboflavin and carnitine; and baclofen for his cogwheel rigidity.[3,5] An electroencephalogram was done which showed evidence of neuronal hyperexcitability. However, the child had

never convulsed and no anti-epileptic drug was started.

The child was thoroughly evaluated for learning disability. His social and behavioral histories were non-contributory and he showed no evidence of hyperactivity or attention deficit. His intellectual ability was tested by the Wechsler's Intelligence Scale for Children-Revised (WISC-R) Indian adaptation test. On the WISC-R his verbal intelligence quotient (I.Q.) was 101, his performance I.Q. was 102 and full scale I.Q. was 102 indicating average intellectual functioning ability. His educational testing was conducted using the Wide Range Achievement Test- Revision 3 (WRAT-3). His WRAT-R blue test scores were: Reading 91, Spelling 100 and Arithmetic 111. On the educational testing he showed evidence of dyslexia, dysgraphia and dyscalculia. He would hold the pencil in an awkward manner and put a lot of pressure while writing. His writing was illegible and he made age-inappropriate spelling mistakes; such as "surpise" for "surprise" and, "belef" for "belief " (Fig. 4). He was advised remedial education for his learning disability and issued a certificate for availing the academic concessions for his schooling.[6]

The child was asked to follow up to assess his response to the recommended therapeutic regimen and to undergo regular remedial education for overcoming his learning disability. The parents were counseled about the condition and asked to bring their second child (a 6 month-old girl) for ruling out GA-I.

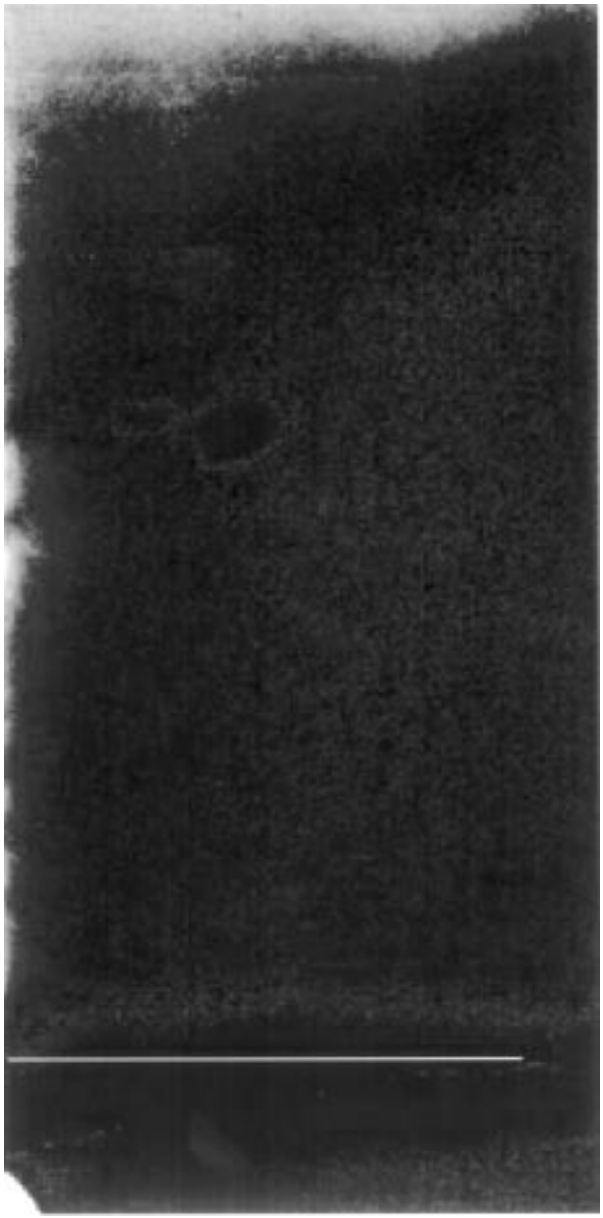

Fig. 2. Urine organic acidogram of "patient" (on right) done by thin layer chromatography showing prominent spot of glutaric acid. On left is the "standard" done simultaneously, which shows spot of standard glutaric acid.

DISCUSSION

GA-I is a rare metabolic neurodegenerative disease which has a "varied" presentation. It has been reported to manifest in infancy or in young children as an acute neurodegenerative illness (often precipitated by an acute febrile illness and hence wrongly diagnosed as "acute encephalitis"), or as a chronic encephalopathy with dystonia and choreoathetoid movements (hence wrongly diagnosed as choreoathetoid cerebral palsy), or even manifesting at a later age.[1-5] Reports of asymptomatic older children and adults with neuroimaging and

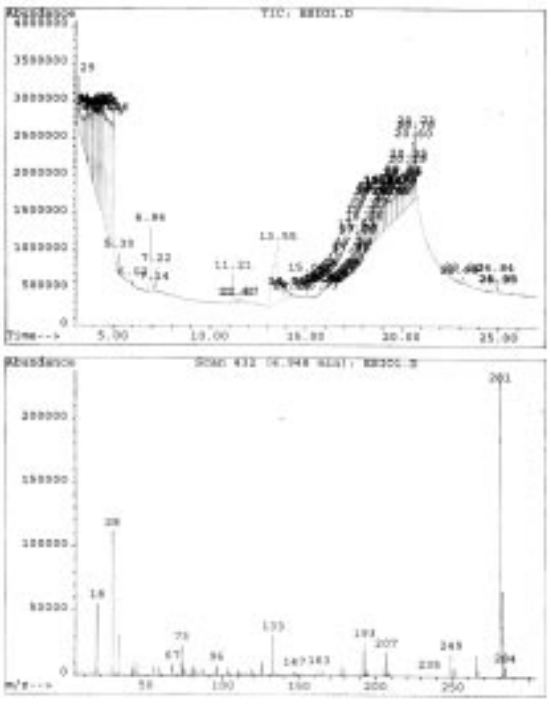

Fig. 3a. Urine organic acid analysis of "patient" done by gas chromatography- mass spectroscopy showing markedly elevated level of glutaric acid at 6.94 minutes, as compared to "standard" shown in Fig 3b.

biochemical abnormalities characteristic of GA-I have also been published.[2, 5]

MRI is now considered the imaging modality of choice. The earliest feature has been reported to be fronto-temporal atrophy beginning as early as the second half of gestation and it is also seen in the asymptomatic phase and it progresses as symptoms develop.[2, 5] Brismar and Ozand [8] reviewed 64 CT or MRI of the brain in glutaric acidemia type I and found that brain atrophy or hypoplasia was seen in 61% and white matter changes in 51% of the cases, open opercula (usually very widely open) and often also wide cerebrospinal fluid spaces anterior to the temporal lobes were seen in 93% of cases. Basal ganglia lesions, presenting as volume loss and high T2 signal in the caudate head and often also the lentiform nucleus bilaterally, were found in 44% of cases.

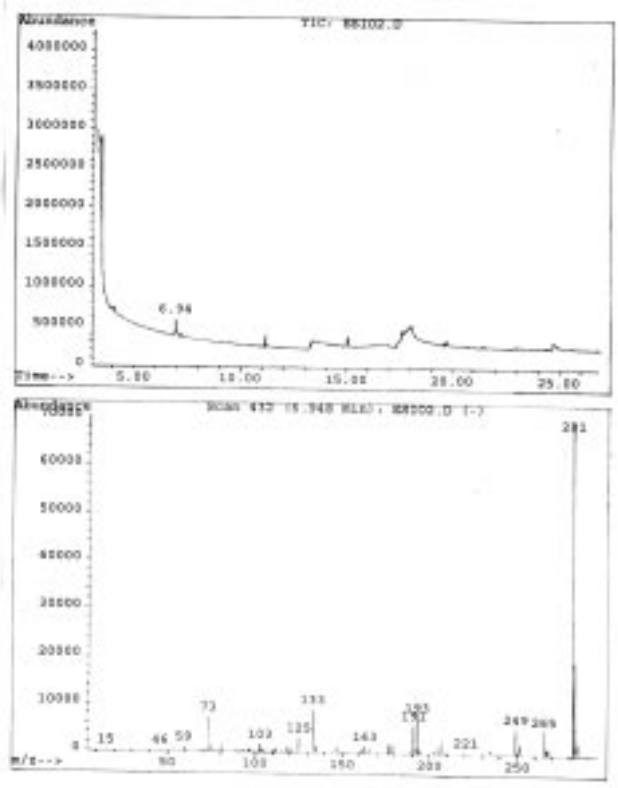

Fig. 3b. Standard glutaric acid analysis done by gas chromatography- mass spectroscopy showing elevated level of glutaric acid at 6.94 minutes.

Fig. 4. Child's illegible handwriting, as seen during his Wide Range Achievement Test, with age-inappropriate spelling mistakes indicating learning disability.

The biochemical hallmark of the disease is the accumulation of glutaric acid and, to a lesser degree, of 3-hydroxyglutaric acid and glutaconic acid in body fluids and tissues.[2, 3]

After initiation of treatment consisting of low-protein diets, special formulas low in lysine and tryptophan, and supplements of riboflavin and L-carnitine, a few patients may show slight improvement, but long term prognosis remains unfavorable. GA-I is still not considered to be a treatable disorder.[2, 3] Megalencephaly has been often reported to be present in the neonatal period, but often becomes less evident with progressive loss of cerebral volume and precedes the neurological disease.[2, 9] Our patient also had a large head noticed during infancy, but further details were not available.

Till date from India, only Murunjan *et al*[10] have reported this disease. They have reported 4 cases of GA-I, aged from 18 months to 4 years, all having seizures and intellectual deterioration. The current patient had manifested at a later age *viz.* 6 years 2 months of age and has had no seizures or intellectual deterioration. To our knowledge, GA-I associated with learning disability has not been reported earlier. Learning disability is a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of skills such as listening, speaking, reading, writing, reasoning or mathematical reasoning or mathematical abilities.[11] These disorders are of 3 types *viz.* dyslexia (difficulty in reading), dysgraphia (difficulty in learning to write) and dyscalculia (difficulty in mathematical reasoning and calculations).[6, 12] Delayed speech and articulation problems are known features of learning disability.[6, 12] These disorders are presumed to be due to central nervous system dysfunction.[6, 12] They are known to occur following metabolic encephalopathies such as Reye's syndrome.[6, 12] Although the precise mechanisms which lead to acquired learning disability are unknown, some of the known diseases and conditions which cause these problems include perinatal events such as prematurity and birth asphyxia; neonatal meningitis, head trauma, tuberous sclerosis, neurofibromatosis, and cranial irradiation.[6, 12] All these diseases and conditions are presumed to damage the brain in a subtle way and this leads to the child having learning disability.[6, 12] We postulate that in the present case the accumulation of glutaric acid and other metabolites was responsible for

the manifestations of learning disability. With the initiation of the recommended therapeutic regimen we aim to control the glutaric acidemia and further neurodegeneration; and with remedial education help the child overcome his learning disability. Long term follow up will be necessary to find out whether these therapeutic and educational interventions do benefit the child.

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REFERENCES

1. Goodman SI, Markey SP, Moe PG, Miles BS, Teng CC. Glutaric aciduria: a "new" disorder of amino acid metabolism. *Biochem Med* 1975; 12 : 12-21.
2. Hoffman GF, Trefz FK, Barth PG *et al.* Glutaryl-coenzyme A dehydrogenase deficiency: a distinct encephalopathy. Pediatrics 1991; 88 : 1194-1203.
3. Hoffman GF, Zschocke J. Glutaric aciduria type I: From clinical, biochemical and molecular diversity to successful therapy. *J Inher Metab Dis* 1999; 22 : 381-391.
4. Brandt NJ, Brandt S, Christensen E, Gregersen N, Rasmussen K. Glutaric aciduria in progressive choreo-athetosis. *Clin Genet* 1978; 13 : 77-80.
5. Amir N, El-Peleg O, Shalev RS, Christensen E. Glutaric aciduria type I: clinical heterogeneity and neuroradiologic features. *Neurology* 1987; 37 : 1654-1657.
6. Kulkarni M, Kalantre S, Upadhye S, Karande S, Ahuja S. Approach to learning disability. *Indian J Pediatr* 2001; 68 : 539-546.
7. Seakins JWT, Ersser RS. Organic Acids. In Smith I, Steakins JWT, eds. *Chromatographic and Electrophoretic Techniques: Volume 1: Paper and Thin Layer Chromatography*, London; William Heinemann Medical Books Ltd, 1976; 253-272.
8. Brismar J, Ozand PT. CT and MR of the brain in glutaric acidemia type I: a review of 59 published cases and a report of 5 new patients. *Am J Neuroradiol* 1995; 16 : 675-683.
9. Iafolla AK, Kahler SG. Megalencephaly in the neonatal period as the initial manifestation of glutaric aciduria type I. J Pediatr 1989; 114 : 1004-1006.
10. Murunjan MN, Kantharia V, Bavdekar SB, Ursekar M. Glutaric aciduria type I. *Indian Pediatr* 2001; 38 : 1148-1154.
11. Hammil DD. On defining learning disabilities: An emerging consensus. *J Learn Disabil* 1990; 23 : 74-84.
12. Shaywitz BA, Shaywitz SE. Learning Disabilities and Attention Disorders. In Swaiman KF, ed. *Pediatric Neurology: Principles and Practice*, St. Louis; CV Mosby Company, 1989; 857-890.