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N R Altman, M J Rovira and M Bauer

AJNR Am J Neuroradiol 1991, 12 (5) 966-968

<http://www.ajnr.org/content/12/5/966.citation>

This information is current as
of April 19, 2024.

Glutaric Aciduria Type 1: MR Findings in Two Cases

Nolan R. Altman,¹ Miguel J. Rovira,² and Mislen Bauer³

Glutaric aciduria type 1 is an autosomal recessive metabolic disorder caused by a deficiency of glutaryl-CoA dehydrogenase. This disorder is characterized by progressive dystonia and dyskinesia. Laboratory evaluation demonstrates excessive levels of glutaric acid urinary excretion as well as absence of demonstrable functional levels of glutaryl-CoA in fibroblast cultures. We present the CT and MR imaging findings of two siblings with biochemically proved glutaric aciduria type 1.

Case Reports

Case 1

This boy was born at term by vaginal delivery without complications; his birth weight was 5487 g. He had an older brother (case 2) who was known to have glutaric aciduria type 1. The patient did well until 4 months of age, when he had a generalized seizure. Motor devel-

opment regressed to the point where he had poor head control. There was generalized hypotonia following the seizures. Physical examination revealed the presence of increased head circumference without dysmorphic features. Biochemical evaluation demonstrated abnormal glutaric acid urinary excretion as well as absence of glutaryl-CoA dehydrogenase activity in cultured fibroblasts.

At age 7 months the patient had MR imaging, which was performed on a 0.3-T imaging system (FONAR, Melville, NY). T1- and T2-weighted spin-echo images (Figs. 1A and 1B) revealed bilateral temporal lobe hypoplasia. The basal ganglia appeared small; however, the degree of myelin deposition was in keeping with the patient's age (Fig. 1C).

Case 2

This boy is 6 years older than the patient described in case 1. He was born at term after an uneventful pregnancy. Birth weight was

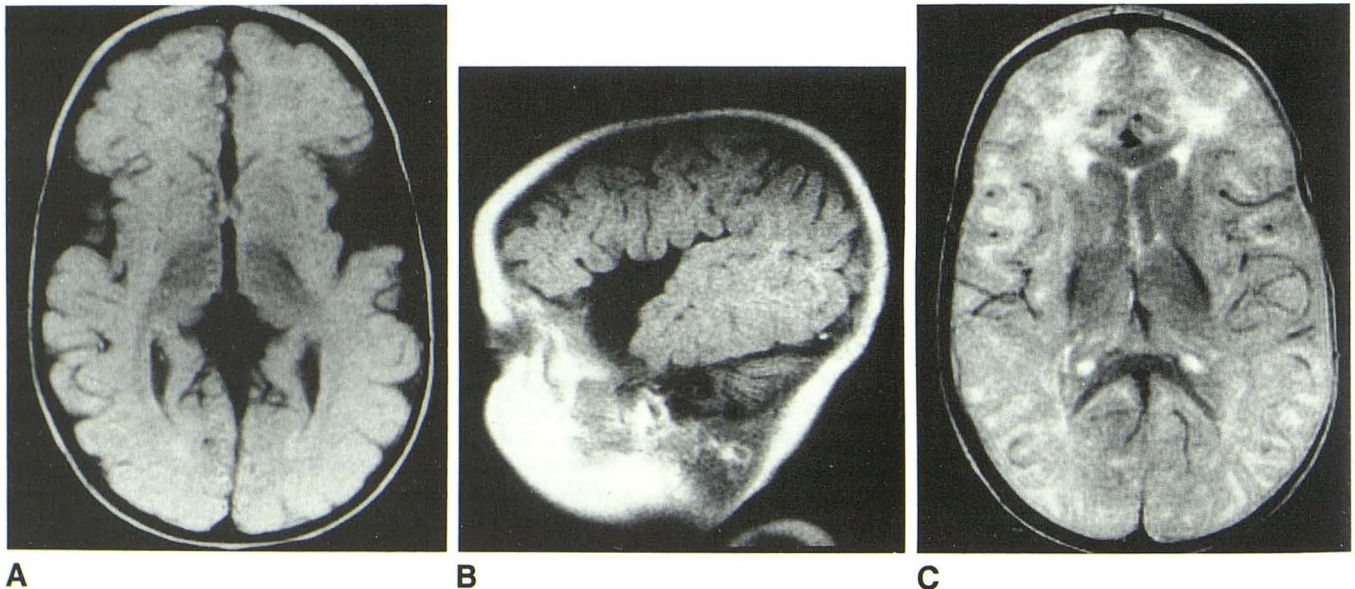


Fig. 1.—Case 1. MR images at age 7 months.

A, Axial T2-weighted first-echo spin-echo MR image (2000/30/2) shows marked expansion of sylvian fissures, identified by enlarged CSF spaces.
B, Sagittal T1-weighted spin-echo MR image (400/16/4) shows absence of part of superior temporal gyrus of left temporal lobe with undulating margins, indicating no mass effect. The prominent sulcal folds of the inferior frontal lobe are seen also.
C, Axial T2-weighted spin-echo MR image (2000/85/2) shows expected myelin deposition for age. The basal ganglia appear small, but signal abnormality is not detected.

Received January 31, 1991; revision requested March 22, 1991; revision received April 8, 1991; accepted April 9, 1991.

¹ Department of Radiology, Miami Children's Hospital, 6125 S. W. 31st St., Miami, FL 33155. Address reprint requests to N. R. Altman.

² Department of Radiology, Jackson Memorial Hospital, Miami, FL 33101.

³ Department of Genetics, Miami Children's Hospital, Miami, FL 33155.

5260 g. He initially presented at 1 year of age with psychomotor developmental delay. He had poor head control and could not sit, crawl, or stand. On initial physical examination the head circumference was at the upper limits of normal; however, it eventually exceeded the 95th percentile. The EEG was normal. Laboratory evaluation demonstrated absence of glutaryl-CoA dehydrogenase activity in cultured fibroblasts. The initial imaging series was performed at age 5 on a GE 9800 CT scanner (GE Medical Systems, Milwaukee, WI) before and after contrast injection. Symmetrically decreased attenuation of the white matter was demonstrated (Fig. 2A), as was bitemporal lobe hypoplasia (Fig. 2B). MR examination performed at 6½ years of age demonstrated bilaterally increased signal intensity of the white matter on T2-weighted images with sparing of the subcortical U fibers. There was also signal abnormality of the bilateral lentiform nucleus (Fig. 2C) and hypoplastic changes of the temporal lobes (Fig. 2D), which were indicated by the normal thickness of the cortex and the coronal orientation of the white matter of the temporal lobe.

Discussion

Glutaric aciduria type 1 is a rare, inherited metabolic disorder, which is proved in the laboratory by excessive levels of glutaric and 3-hydroxyglutaric acids in the urine, reduced serum carnitine, and absence of demonstrable functional levels of glutaryl-CoA of fibroblasts or leukocytes. Glutaric aciduria type 2 is caused by a deficiency of electron transfer flavoprotein, or ubiquinone oxidoreductase. To date only 20 cases of neuroimaging studies of glutaric aciduria type 1 have been described. Our cases appear to be representative of what has been observed.

An early finding in the course of the disease is hypoplasia of the frontotemporal regions, which has been confirmed by CT and MR examinations [1-6]. This is usually bilateral and appears as enlargement of the CSF spaces anterior to the

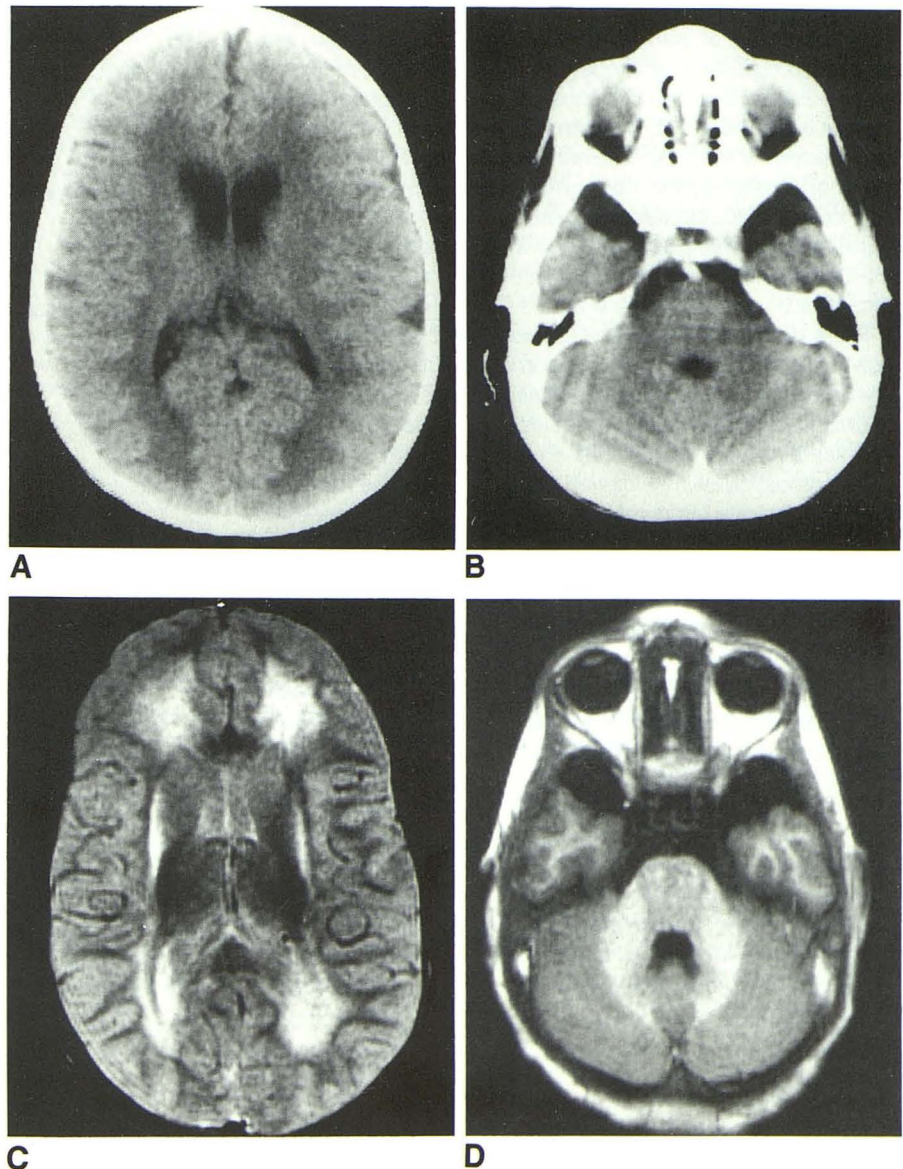


Fig. 2.—Case 2. CT images without contrast at age 5 years (A and B) and MR images at age 6½ years (C and D).

A, CT scan shows diffuse low attenuation of white matter.

B, CT scan shows prominence of CSF spaces about the temporal poles, indicating temporal lobe hypoplasia.

C, Axial T2-weighted spin-echo MR image (2000/85/2) shows demyelinated white matter with high signal intensity. The basal ganglia are involved.

D, Axial inversion recovery MR image (1500/350/28/1) shows coronally oriented bitemporal white matter and normal thickness of cortical surfaces.

temporal lobes. Whether this represents temporal lobe atrophy or hypoplasia of the temporal operculum is uncertain. The increased CSF spaces also appear similar to middle cranial fossa cysts associated with temporal lobe hypoplasia. Hypoplasia or hypogenesis of the temporal lobe has been described as those temporal lobes that have a normal cortical thickness and coronally oriented white matter with loss of parenchyma and associated surrounding dilated CSF space [7]. Our cases conformed to this description so we decided to refer to these areas as hypoplastic rather than atrophic. A recent report demonstrates interval diminution of the width of the sylvian fissure and the CSF space about the temporal pole on CT over a 10-month period following treatment with oral carnitine and dietary protein restriction [8]. This may represent interval development of the temporal lobe. Surgical or autopsy correlation is needed to further address this issue. The other consistent finding is presence of bilateral symmetrical demyelination [9, 10]. One other report [11] describes signal abnormality within the neostriatum, as was seen in our case 2.

The mechanism of toxicity is not well understood, as in many of the cases of organic acidopathies. One theory implicates inhibition of neuronal glutamate decarboxylase with decreased GABA biosynthesis by the accumulated metabolic intermediates, but how this causes neuronal degeneration is still not understood [1]. Biochemical analysis of the brains of two children with glutaric aciduria type 1 disclosed elevated levels of glutaric acid in the frontal cortex and basal ganglia, very low glutaric acid decarboxylase activity in the substantia nigra, and extremely low GABA in the caudate and putamen [2]. Glutaric acid decarboxylase is inhibited by glutaric acid *in vitro*, which is relevant to the above [2].

There is, however, a clinical variability among homozygous individuals affected with this disorder. Some appear to be asymptomatic; somehow, genetically polymorphic protective mechanisms spare these individuals. Correlation with CT and examinations also reveal that an overlap exists. Asymptomatic homozygotes may have normal examinations but some may demonstrate temporal lobe hypoplasia [2]. Demyelination has rarely been demonstrated in the asymptomatic individual [4]. Progression of neuroradiologic findings, however, appears to occur in the symptomatic patient [2]. Treatment of symptomatic individuals consists of administration of a low lysine diet, riboflavin, and L-carnitine, with limited effects [2]. Others [3] have used Lioresal, an analogue of GABA [3]. Follow-up imaging of treated individuals demonstrates a clearly delayed progression of the disease, which again be-

comes progressive upon cessation of diet. Partial regression of findings has recently been described in one case [8]. Prophylaxis in asymptomatic kindred is controversial, as results show no consistent clinical or biochemical improvement [6].

Prenatal diagnosis of glutaric aciduria type 1 can be made by determining the glutaric acid concentration in amniotic fluid and glutaryl-CoA dehydrogenase activity in cultured amniotic cells [2]. This is important in counseling parents with one affected child.

In summary, the neuroradiologic findings of bifrontotemporal hypoplasia, demyelination, and changes of the basal ganglia in a child with megalencephaly should raise the suspicion of glutaric aciduria type 1. However, this disorder can produce similar biochemical findings in both clinically asymptomatic and symptomatic individuals. Serial neuroradiologic findings of progression of demyelination can be seen in the symptomatic individuals. Treatment has resulted in delayed progression and partial regression. Serial examinations are important to gauge the response to therapy.

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