(*Acta Paediatr Jpn 1992*; 34: 409 ~ 415)

Neuroradiological Findings in Glutaric Aciduria Type I: Report of Four Japanese Patients

Hiroyuki Nagasawa, M.D.,[1] Seiji Yamaguchi, M.D.,[1] Yasuyuki Suzuki, M.D.,[1] Masanori Kobayashi, M.D.,[2] Yoshiro Wada, M.D.,[2] Keiko Shikura, M.D.,[3] Satoshi Shimao, M.D.,[4] Toshio Okada, M.D.[4] and Tadao Orii,[1] M.D.

[1]*Department of Pediatrics, Gifu University School of Medicine, Gifu;* [2]*Department of Pediatrics, Nagoya City University Medical School, Nagoya;* [3]*Department of Pediatrics, Juntendo University Izu-Nagaoka Hospital, Izu-Nagaoka; and* [4]*Department of Pediatrics, Toyama Medical and Pharmaceutical University Faculty of Medicine, Toyama, Japan*

We examined neuroradiological computerized tomography (CT) findings and the clinical course of four Japanese children with glutaric aciduria type I (GA1) whose enzyme activity of glutaryl-CoA dehydrogenase was undetectable. Brain CT in all cases examined showed low density white matter, fluid collection in bilateral frontotemporal regions (particularly surrounding the Sylvian fissures), enlargement of the lateral ventricles and slight atrophy of the basal ganglia. Although these findings seemed to be characteristic for GA1, they were unlikely to be more extended, at least over 2 years after infancy. The low density white matter was observed more evidently in the neonatal or early infantile periods than in later periods. The degree of enlargement of fissures in bilateral frontotemporal regions about the Sylvian fissures appeared to correlate with the severity of symptoms such as dystonia or choreoathetosis. Magnetic resonance images (MRI) in one case showed bilateral linear-shaped low intensity in areas of the external capsules and putamen on a T1-weighted image. These CT and MRI findings, as well as clinical symptoms such as choreoathetosis or dystonia, may suggest that metabolic abnormalities in GA1, such as glutaconate, are toxic to the extrapyramidal tract system in the central nervous system, and that the clinical symptoms of the patients are attributable to atrophy of basal ganglia. Brain CT may be useful in diagnosis and evaluation of the clinical course of GA1 patients.

Key Words

Computerized tomography, Glutaric aciduria type I, Inherited metabolic disorders of organic acid, Magnetic resonance imaging

Received July 16, 1991
Revised January 6, 1992
Accepted January 7, 1992

Correspondence address: Hiroyuki Nagasawa, Department of Pediatrics, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan.

Introduction

Glutaric aciduria type I (GA1), first reported in 1975 [1], is an inherited disorder of lysine, hydroxylysine and tryptophan metabolism that is caused by a deficiency of glutaryl-CoA

dehydrogenase. This disease is characterized by massive urinary excretion of glutarate and increased amounts of 3-hydroxyglutaconate and glutaconate. It is clinically characterized by the appearance in infancy of progressive neurological symptoms such as dystonia or choreoathetosis. Approximately 50 cases with GA1 have already been reported, and clinical heterogeneity of symptoms has been described. Asymptomatic patients with the disease were also reported [2]. Recently, characteristic findings in the cerebral CT have been noted, but only a few reports described their course. We describe here the changes of cerebral CT findings in relation to clinical features in four Japanese patients with GA1.

Case Reports

The clinical features of the four patients are summarized in Table 1.

Patient 1

A girl was diagnosed as having GA1 following urinary organic acid analysis using gas chromatography and mass spectrometry (GC/MS) at the age of 7 months. She was born after full-term gestation to unrelated parents, with normal delivery and an uneventful neonatal period. Her head control was unsteady at the age of 4 months. At 5 months, she presented with sleep disturbance and irritability. She was admitted to hospital at 8 months of age. Dietary restriction (protein intake 1.5 g/kg per day) with vitamin B2 therapy (50 mg/kg per day) failed to improve the neurological symptoms. Since bacrofen (GABA analogue, 2 mg/kg per day) was administrated at the age of 8 months, her symptoms of sleep disturbance and irritability have remarkably improved. However, other neurological symptoms, such as dystonia and choreoathetosis, gradually progressed. The administration of sodium valproate, which was considered to be an inhibitor of GABA degradation, and clofibrate, a hypolipidemic drug, had very little clinical effect. Oral supplementation of L-carnitine resulted in an elevation of free carnitine levels in blood and urine, but produced no improvement in clinical symptoms. The patient could not roll over or sit unsupported at 5 years. She died of sudden death at her home a few days after having a cold at the age of 5 years.

Patient 2

A boy was born to unrelated parents after a normal pregnancy, and had an uneventful neonatal period. He could sit alone at the age of 6 months. Vomiting and diarrhea followed by unconsciousness and convulsions occurred shortly after vaccination for poliovirus. At 7 months he was diagnosed as GA1 by a carboxyl acid analyser and GC/MS. He presented with dystonia and athetosis, as did Patient 1. Vitamin B2 therapy did not improve his symptoms. Administration of bacrofen (2 mg/kg per day) improved the neurological symptoms only marginally. He was able to roll over somehow and understand some words at the age of 5 years.

Table 1. Clinical features of the four patients

	Case 1	Case 2	Case 3	Case 4
Sex	F	M	M	M
Age at onset (months)	4	6	2	2
Age at diagnosis (months)	7	6	3	2
Initial symptoms or findings	poor head control, irritability	convulsion, unconsciousness	enlarged head, convulsion	enlargement of ventricles
Development age (years)	5	5	3	2
Walking alone	–	–	+	–
Sitting alone	–	–	+	–
Rolling over	–	–	+	–
Word understanding	+	+	+	+
Speaking	–	–	+	–
Mental retardation	severe	severe	mild	moderate
Urinary excretion of glutarate* (μg/mg creatinine)	5271	2185	3626	5716

*Normal value ($n = 20$): 0–29 μg/mg creatinine.

Patient 3

A boy was born to unrelated parents as the second child of fraternal twins at 27 weeks of gestation. His birthweight was 998 g, while that of his twin sister was 935 g. He was hospitalized to a newborn intensive care unit and underwent mandatory ventilation for respiratory distress syndrome. His head circumference was enlarged at 2 months of age (corrected age, 35 weeks of gestation), and tonic convulsion occurred at 3 months of age (corrected age, 0 months). The diagnosis of GA1 was made by organic acid analysis using GC/MS at 4 months (corrected age, 1 month). Low protein diet therapy and the administration of L-carnitine and bacrofen were commenced at the age of 5 months (corrected age, 2 months). He could babble at 7 months (corrected age, 4 months), and began to walk alone at 22 months (corrected age, 19 months). He could run and understand words at 3 years. Compared with his sister (who from the enzyme assay was suspected of being a heterozygote of the disease), no definite athetosis, slight hypotonia or mild developmental delay were noted. From the enzyme assay, he was suspected to be a heterozygote of the disease.

Patient 4

A boy, born to unrelated parents, presented with initial vomiting and idiopathic hyperbilirubinemic episodes in the neonatal period. At that time, a cranial ultrasound examination revealed enlarged ventricles. The diagnosis of GA1 was made by GC/MS screening at the age of 2 months. He received bacrofen from 3 months of age without presenting with athetosis or dystonia. He could crawl on all fours and understand several words, but at 2 years he cannot speak. Organic acid and acylcarnitine profiles were reported previously [4].

Glutaryl-CoA dehydrogenase activities of the four patients and their families were determined as previously described [5] using peripheral leucocytes, lymphocytes or cultured skin fibroblasts. Severely reduced activity of glutaryl-CoA dehydrogenase was detected in the four patients, and the activi-ties in all the parents were found to be intermediate values between those of the patients and normal controls, suggesting heterozygosity.

Results

The course of the CT findings in these patients was examined.

Patient 1

Brain CT at the age of 6 months showed low density white matter and striking fluid collection of the frontotemporal regions, especially in the temporal lobes (Fig. 1). Mild enlargement of the lateral ventricles and slight atrophy of the basal ganglia were also noted. Enlargement of the lateral ventricles at the age of 12 months was more prominent compared with that at 6 months, but has not changed after infancy. The other CT abnormalities also did not change, at least until the age of 5 years when the last examination was performed. MRI examined at 4 years showed a linear-shaped low intensity area about the external capsule and putamen on the T1-weighted image (Fig. 1).

Patient 2

Brain CT at the age of 7 months showed low density white matter, fluid collection in the frontotemporal regions (most evident in the temporal lobes), enlargement of the ventricles and atrophy of the basal ganglia as in Patient 1 (Fig. 2). Enlargement of the lateral ventricles appeared to be relatively stressed at 16 months compared with at 7 months, but has not enlarged since. Other abnormalities in the CT findings were not evident until at least 2 years of age.

Patient 3

Brain CT performed at the ages of 3, 9 and 12 months (corrected age 0, 6 and 9 months, respectively) showed fluid collection in the frontotemporal regions, enlargement of the ventricles and atrophy of the basal ganglia (Fig 3). However, these find-ings seemed to be milder than those of the other three patients. Diffuse attenuation of the density of the cerebral white matter was evident at 3 months, but was less extensive at later examinations.

Patient 4

Diffuse attenuation of the density of the cerebral white matter was observed at 4 weeks,

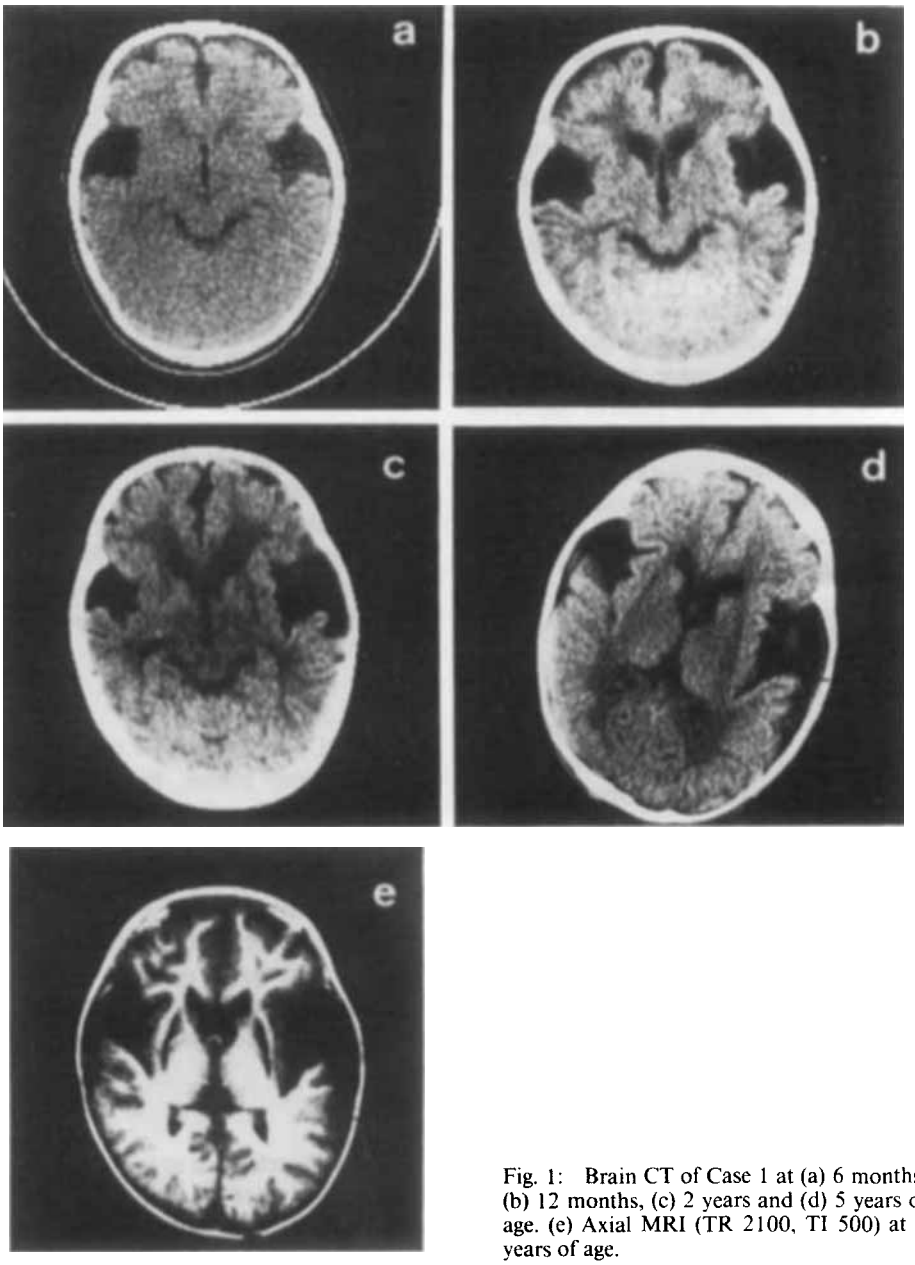

Fig. 1: Brain CT of Case 1 at (a) 6 months, (b) 12 months, (c) 2 years and (d) 5 years of age. (e) Axial MRI (TR 2100, TI 500) at 4 years of age.

but was not so evident at later examinations, as with Patient 3 (Fig. 4). Brain CT scans at the ages of 8 and 12 months showed remarkable atrophy (especially in temporal regions), moderate enlargement of the ventricles and slight atrophy of the basal ganglia (not shown).

Discussion

GA1 is a disorder of the organic acid metabolism due to a deficiency of glutaryl-CoA dehydrogenase activity. According to previous case reports, clinical manifestations have been de-

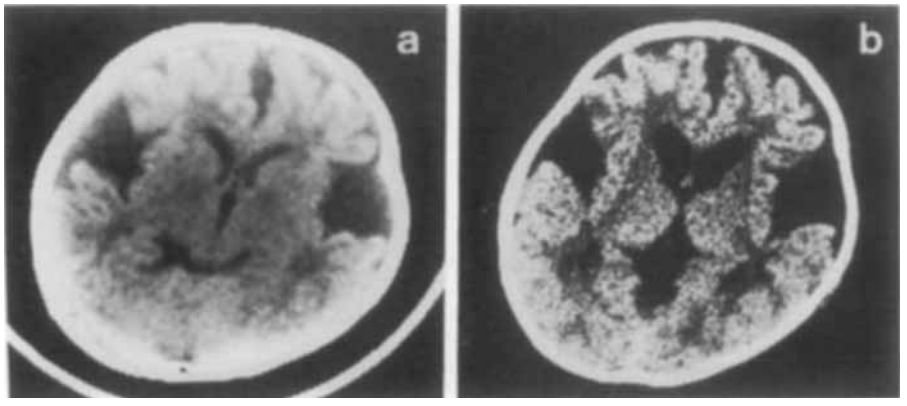

Fig. 2: Brain CT of Case 2 at (a) 7 months and (b) 16 months of age.

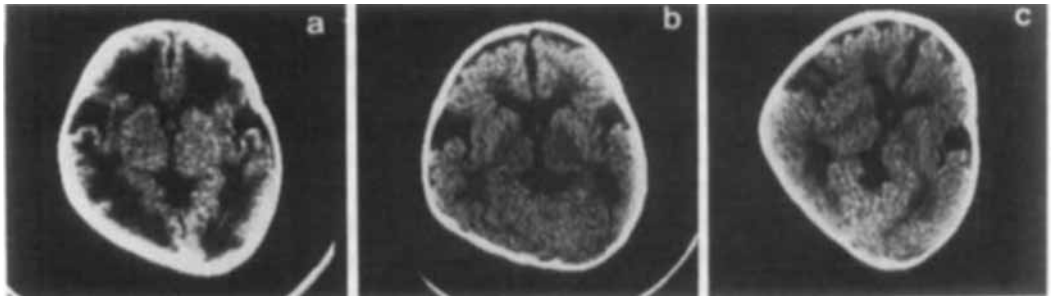

Fig. 3: Brain CT of Case 3 at (a) 3 months (corrected age 0 month), (b) 9 months (6 months) and (c) 12 months (9 months) of age.

scribed as: (1) no clinical symptoms associated with the disease in the neonatal period; (2) some neurological symptoms in early or middle infancy, such as dystonia or choreoathetosis, that are often progressive; and (3) a relatively milder degree of mental retardation compared with that of motor retardation.

Common abnormalities in the brain CT findings in the four patients included low density white matter, enlarged ventricles, generalized cortical atrophy (particularly in the temporal regions) and slight atrophy of the basal ganglia. Since these observations have also appeared in some previous papers [3,6–12], they are possibly characteristic findings in brain CT of patients with GA1.

Marked and diffusely attenuated density in the cerebral white matter might be a characteristic CT finding in the early stage of the disease [12]. These findings were noted at 3 months (2 weeks, corrected age) and at 4 weeks in patients 3 and 4, respectively, but were unremarkable in both cases at later examinations. Attenuation of the density of the white matter in brain CT may be a characteristic of the disease in neonates or early infancy. According to the time courses of the CT in the four patients, these abnormalities seemed to become gradually more evident until about 1 year of age, but did not progress after this period. At present, this observation has not been explained. However, it may be possible that the development of the brain is more dynamic in the infantile period.

Common features in the time course of the brain CT findings in this disease may possibly be as follows: (1) diffuse attenuation of the density of the cerebral white matter in the neonatal period and early infancy; (2) the attenuation becomes gradually less extensive; (3) enlargement of the ventricles and generalized

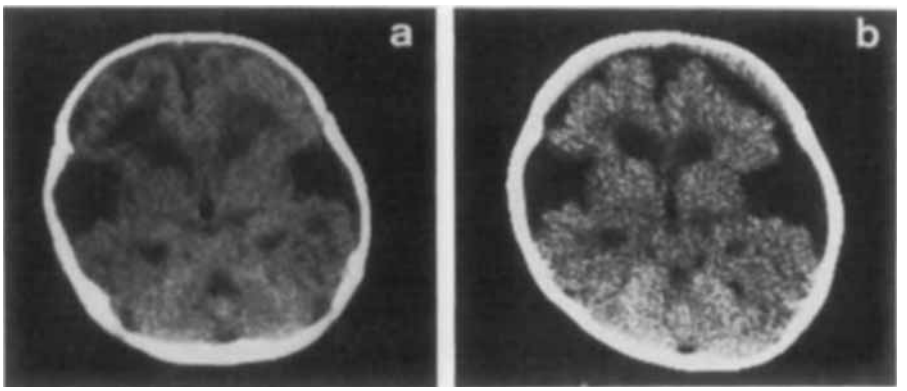

Fig. 4: Brain CT of Case 4 at (a) 4 weeks and (b) 4 months of age.

brain atrophy become evident in infancy; and (4) no extensive findings have been made after infancy.

Considerable differences in the clinical features of the disease have been reported [2,13]. In this study, patients 1 and 2 presented with severe symptoms, while patients 3 and 4 presented with mild or intermediate symptoms. Severe widening of Sylvian fissures was observed in patients 1, 2 and 4, but not in Patient 3, whose symptoms were the mildest of the four. The clinical severity of the disease might correlate with the degree of the abnormalities, such as enlargement of the ventricles and cortical atrophy in CT findings. However, enlargement of ventricles has been reported in asymptomatic patients with typical brain CT findings [2].

In MRI findings, a linear-shaped low intensity area of the putamen and external capsule (T1-weighted image) was observed in Patient 1. In one study, temporal lobe atrophy and fibrosis and hyperlucency of the lateral aspect of the caudate nucleus was considered to possibly be indicative of basal ganglia necrosis [14]. In one autopsy case, the putamen disclosed bilateral shrinkage and grey discoloration, and the putamen and lateral margins of the caudate displayed chronic degeneration with severe neuronal loss and fibrous gliosis [15]. According to another autopsy report, gross examination demonstrated some shrinkage of the caudate and putamen anteriorly, and microscopic examination of the caudate nucleus and putamen showed severe loss of nerve cells and fibers with a proliferation of astrocytes [9]. These findings may be compatible with the MRI findings for Patient 1 and a previously reported case [14], and clinical symptoms such as dystonia or choreoathetosis may be attributed to atrophy in basal ganglia. On the other hand, the relation between the atrophy of temporal lobes and the clinical symptoms remain unclear.

The clinical symptoms, the effectiveness of the GABA analogue (a suppressive neurotransmitter in basal ganglia), and these abnormalities in brain CT and MRI findings suggest that the abnormal metabolites in GA1 are toxic mainly to the extrapyramidal tract system in the central nervous system.

References

1. Goodman SI, Markey SP, Moe PG et al. Glutaric aciduria: A 'new' disorder of amino acid metabolism. Biochem Med 1975; 12: 12–21.
2. Amir N, Elpeleg ON, Shalev RS et al. Glutaric aciduria type I: Enzymatic and neuroradiologic investigations of two kindreds. J Pediatr 1989; 114: 983–989.
3. Yamaguchi S, Orii T, Yasuda K et al. A case of glutaric aciduria type I with unique abnormalities in the cerebral CT findings. Tohoku J Exp Med 1987; 151: 293–299.
4. Matsumoto M, Matsumoto I, Shinka T et al. Organic acid and acylcarnitine profiles of glutaric aciduria type I. Acta Pediatr Jpn 1990; 32: 76–82.
5. Christensen E, Brandt NJ. Studies on glutaryl-CoA dehydrogenase in leucocytes, fibroblasts and amniotic fluid cells. The normal enzyme and the mutant form in patients with glutaric aciduria. Clin Chim Acta 1978; 88: 267–276.

6. Amir N, El-Peleg O, Shalev RS et al. Glutaric aciduria type I: Clinical heterogeneity and neuroradiologic features. Neurology 1987; 37: 1654–1657.
7. Bennet MJ, Marlow N, Pollitt RJ et al. Glutaric aciduria type 1: Biochemical investigations and postmortem findings. Eur J Pediatr 1986; 145: 403–405.
8. Dunger DB, Snodgrass GJAI. Glutaric aciduria type I presenting with hypoglycaemia. J Inher Metab Dis 1984; 7: 122–124.
9. Leibel RL, Shih VE, Goodman SI et al. Glutaric acidemia: A metabolic disorder causing progressive choreoathetosis. Neurology 1980; 30: 1163–1168.
10. Seccombe DW, James L, Booth F. L-Carnitine treatment in glutaric aciduria type I. Neurology 1986; 36: 264–267.
11. Stutchfield P, Edwards MA, Gray RGF et al. Glutaric aciduria type I misdiagnosed as Leigh's encephalopathy and cerebral palsy. Dev Med Child Neurol 1985; 27: 514–518.
12. Yager JY, McClarty BM, Seshia SS. CT-scan findings in an infant with glutaric aciduria type I. Dev Med Child Neurol 1988; 30: 808–811.
13. Haworth JC, Booth FA, Chudley AE et al. Phenotypic variability in glutaric aciduria type I: Report of fourteen cases in five Canadian Indian kindreds. J Pediatr 1991; 118: 52–58.
14. Lipkin PH, Roe CR, Goodman SI et al. A case of glutaric acidemia type I: Effect of riboflavin and carnitine. J Pediatr 1988; 112: 62–65
15. Goodman SI, Norenberg MD, Shikes RH et al. Glutaric aciduria: Biochemical and morphologic considerations. J Pediatr 1977; 90: 746–750.