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CT and MR of the Brain in Glutaric Acidemia Type I: A Review of 59 Published Cases and a Report of 5 New Patients

Jan Brismar and Pinar T. Ozand

PURPOSE: To identify a pattern of findings on CT or MR of the brain in glutaric acidemia type I typical enough to permit a correct diagnosis. **METHODS:** Clinical history and findings and brain CT and MR results in 59 previously reported patients (MR in 12) and in 5 new patients (all examined with MR and 3 also with CT) were reviewed. **RESULTS:** In half the patients macrocephaly was present, and in half the onset was acute, often following infection and mimicking encephalitis. Although brain atrophy or hypoplasia was found in 61% and white matter changes in 51% of the patients, open opercula (usually very widely open) and often also wide cerebrospinal fluid spaces anterior to the temporal lobes were seen in 93%. 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% and extracerebral fluid collections in 7 of 64 patients. **CONCLUSION:** The finding of very widely open opercula suggests glutaric acidemia type I, and if combined with basal ganglia lesions is almost pathognomonic, especially in a child with macrocephaly.

Index terms: Acidemia; Brain, computed tomography; Brain, magnetic resonance; Pediatric neuroradiology

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Glutaric acidemia type I is one of the least rare organic acidemias; prevalence figures as high as 1 in 30 000 have been suggested (1). The number of diagnosed cases is, however, still low, because the presentation is very variable and often confusing. The disease may sometimes have a slowly progressive course and may present merely as mental retardation. More typically, the disease presents in infancy, mimicking acute encephalitis, leaving a previously healthy child severely handicapped with global dystonia, perhaps spastic quadriplegia, and choreoathetosis (2–4). Many thus-affected children are probably to be found in nursing homes with diagnoses of postencephalitic syn-

drome, severe cerebral palsy, and mental retardation (4, 5). Some patients may reach adulthood without any manifestations of the disease (3, 4). This variability in presentation and severity of disease may occur within the same genetic isolate and even within the same family (3, 4).

Neuroradiologic findings in some 60 patients with glutaric acidemia type I have been reported (2–4, 6–22), often as brief comments in articles dealing mainly with clinical or biochemical findings. Magnetic resonance (MR) results have been reported in 12 patients (2, 3, 13, 15–18, 21, 22). Some reports suggest that early therapy may arrest or even reverse the disease process (16, 23). The aim of this article is to review 5 new cases together with previous reports on neuroradiologic findings in glutaric acidemia type I, to define early computed tomographic (CT) and MR changes, which in some cases may occur even before the onset of neurologic symptoms. Such information might help radiologists recognize the disease in an asymptomatic child, evaluated for macroceph-

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aly (13, 14), before irreversible brain damage has developed.

Subjects and Methods

During the last 5 years, more than 150 patients at our institution have received diagnoses of different organic acidemias, 6 of those of glutaric acidemia type I. The diagnoses were established through a combination of tandem mass spectroscopy of blood samples, mass spectroscopy and gas chromatography of urine, and different enzymatic and provocation studies. In 5 of the patients with glutaric acidemia type I, MR imaging, and in 3 also CT of the brain, was performed. The clinical and demographic data on our patients are presented in Table 1.

For CT, 10-mm-thick contiguous sections were obtained. The MR studies were performed on a 1.5-T device using T1-weighted (600/20/2 [repetition time/echo time/excitations]) and dual-echo T2-weighted (2000/30-40,80/2) axial sections gapped 0 to 2.5 mm (depending on head size) and T1-weighted sagittal sections. The size of the cerebrospinal fluid (CSF) spaces and the extent of the white matter changes were retrospectively, subjectively, and nonblindly graded as mild, marked, or severe.

Results

The neuroradiologic findings in our five patients are presented in Table 1 and also in Figures 1 through 3. In all five patients the opercula were bilaterally markedly to severely widened. This widening in all but one of the patients was clearly out of proportion to the width of the remainder of the extracerebral CSF space, which was mildly to markedly widened in all but one of the patients (Fig 1). In all five children basal ganglia were involved, although one initially had normal-appearing basal ganglia at CT. The basal ganglia changes seem to manifest first as increased T2 signal without volume loss bilaterally in the caudate heads and lentiform nuclei (Figs 1B and 2B). Volume loss of the caudate head follows (Figs 2C and 3A), and the changes then progress to involve both the caudate and lentiform nuclei, with volume loss and increased T2 signal (Figs 2D and 3D). High T2 white matter changes were found in four of the children, ranging from mild to severe (Fig 3D) and in all patients were confluent. In the least affected child (patient 4), the changes had a mainly periventricular distribution and were most pronounced in the trigonal regions; in two patients (patients 2 and 5), both the periventricular white matter and the most peripheral white matter were involved with some sparing of

a zone in between, whereas in patient 3, all subcortical white matter was severely involved.

Discussion

We have identified and reviewed reports on 59 patients with glutaric acidemia type I, examined with CT and/or MR of the brain; MR was performed in 12 patients. The neuroradiologic findings, the case histories, and the clinical findings in these reports are often presented briefly and incompletely (because the articles were published to illustrate some other point), and usually some of the reviewed cases therefore have to be discarded when analyzing a certain finding. We have not been able to find any conclusive review of the radiologic findings in glutaric acidemia type I; thus, the frequency of the different radiologic findings and their relation to the severity of the disease have not been known.

Glutaryl-coenzyme A is an intermediary product in the metabolism of the amino acids lysine, hydroxylysine, and tryptophan. The further decarboxylation of glutaryl-coenzyme A to crotonyl-coenzyme A (which is then metabolized to acetyl-coenzyme A) is dependent on the enzyme glutaryl-coenzyme A dehydrogenase. Deficiency of this enzyme, inherited in an autosomal-recessive manner, causes glutaric acidemia type I; the metabolic block leads to an accumulation and excretion of 3-hydroxyglutaric and glutaconic acids. (Glutaric aciduria type II, also known as multiple acyl-coenzyme A lyase deficiency, is an entirely different disease, associated with fatty acid metabolism, and will not be further discussed.)

The most striking finding at brain imaging in glutaric acidemia type I is the presence of very wide CSF spaces anterior to the temporal lobes and within the sylvian fissures. This was not noted in the earlier reports on neuroimaging in glutaric acidemia type I (6-10) and was first described as a characteristic finding in glutaric acidemia type I in 1987 (11, 24). Widening of the sylvian fissures has since proved to be a very common feature in glutaric acidemia type I and was found in 48 of 51 patients reported in 1988 or later, as well as in our 5 patients. The anomaly may range from a complete lack of operculation with gross hypoplasia of the temporal lobes and with huge CSF spaces in front of the temporal lobe (Figs 2 and 3) to widening of the sylvian fissures in proportion to the promi-

TABLE 1: Clinical history and findings and brain CT and MR results in five children with glutaric aciduria type I

Patient	Sex/Age	Exam	Macrocephaly	Mode of Onset	Clinical Findings	Neuroradiologic Findings				
						Atrophy or Hypoplasia	Open Opercula	White Matter Disease	Basal Ganglia Changes	Extracerebral Collections
1	F/14 mo	MR	Relative	Healthy until 14 mo, then fever, enteritis, seizures, followed by severe psychomotor retardation	Dystonic posturing, choreoathetosis, spastic quadriplegia, clinical deterioration despite diet	None	++	None	No volume loss, increased T2 intensity in lentiform nucleus and caudate head	None
2	M/7 mo	MR	None	Healthy until 3 mo, when after fever and vomiting, seizures and poor head control developed; increasing seizure frequency, regression of milestones	At 7 mo, severe head lag, hypotonia, unable to follow light, no dystonia, normal tendon reflexes; at 15 mo, dystonia, scissoring of legs, developmental age of 3 mo, then on diet leading to improvement; can stand and has begun talking	++	++	None	Slightly increased T2 signal, but no volume loss in lentiform and caudate nuclei bilaterally	None
	8 mo later	CT				++	++	None	Slight loss of volume in caudate heads	None
	2 mo later	MR				++	++	++	Volume loss and high T2 intensity in caudate heads and lentiform nuclei	None

(Table continues)

Note:—+ indicates mild; ++, marked; and +++, severe changes.

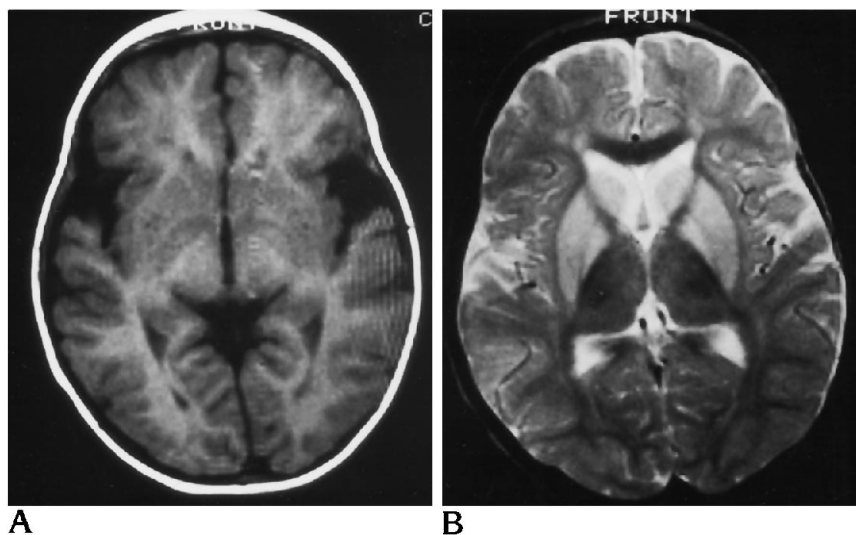


Fig 1. Case 1. Previously healthy 14-month-old girl who, after fever and enteritis, became severely debilitated with choreoathetosis and spastic quadriplegia.

A, MR T1-weighted section shows markedly widened sylvian fissures with wide open opercula, unlike the otherwise normal wide CSF spaces.

B, MR T2-weighted section demonstrates increased intensity but no volume loss in the lentiform nucleus and the caudate head.

nence of other extracerebral CSF spaces (patient 4). Operculation normally takes place during the last trimester of gestation (25), and the presence of this anomaly thus suggests that the toxic effects in glutaric acidemia type I start already in utero. It has been suggested that the bilateral temporal fluid collections may be caused by arachnoidal cysts of the temporal fossa (17), but this has not been proved. The open opercula sign in glutaric acidemia type I is not correlated to the severity of the disease. Thus, of the 4 published patients who were explicitly mentioned to lack the sign, at least 2 (15, 17) were severely disabled, whereas, on the other hand, the sign was present in all 5 clinically healthy patients (3, 13). Although in 3 published patients (2, 3, 20), the widening of the opercula became more pronounced with age, in 1 despite treatment (20), in 1 of our patients (patient 4), as well as in 1 published case (14), findings improved after treatment.

Atrophy or hypoplasia of brain tissue other than the temporal lobes was present in 38 of 62 patients, in 3 only mild. The atrophy was described as progressive in 5 patients (2, 10, 20, 24), whereas in our patient 4 and in 2 other patients, findings improved (16, 18) with time and diet.

Extracerebral fluid collections, other than those anterior to the temporal lobes, were observed in seven children (6, 14, 17, 20, 22, 24), in two only unilaterally (20, 24). These collections were described as wide CSF spaces (14), subdural collections (3, 20), extracerebral fluid

collections (6, 22), or bilateral frontoparietal subdural hematomas (17). In one the collections expanded the adjacent cranial vault (22). In two patients the collections were transient, in one present at 1.5 years but not at 1 or 2.5 years (3), and in one seen at 10 months but not at 21 months (6). In two children the collections were shunted and evacuated by trephination, respectively (17). Both of these children later developed hydrocephalus that required shunting.

In 49 of the patients the presence or absence of white matter changes was addressed. In 25 patients the white matter was normal; in 24 white matter changes were found; white matter was usually described as of diffusely low density on CT or high T2 intensity on MR. No correlation was found between the occurrence of white matter changes and the clinical severity of the disease. In 2 of the patients white matter changes were seen only as transient white matter edema in the neonatal period (12, 24). In some children progressive demyelination was observed (10, 20).

Basal ganglia changes were observed in 28 of the 64 patients, including all 5 of our patients; again, no obvious correlation to the severity of the disease was found. The changes were described as mild and transient lenticular nucleus hypodensity in 2 children (8) and as volume loss of the caudate nuclei in 4 (2, 3, 16); the remainder, as in our patients, were found to involve also the lentiform nuclei (4, 15, 18, 21). Our results suggest that the basal ganglia changes first present as increased T2 intensity

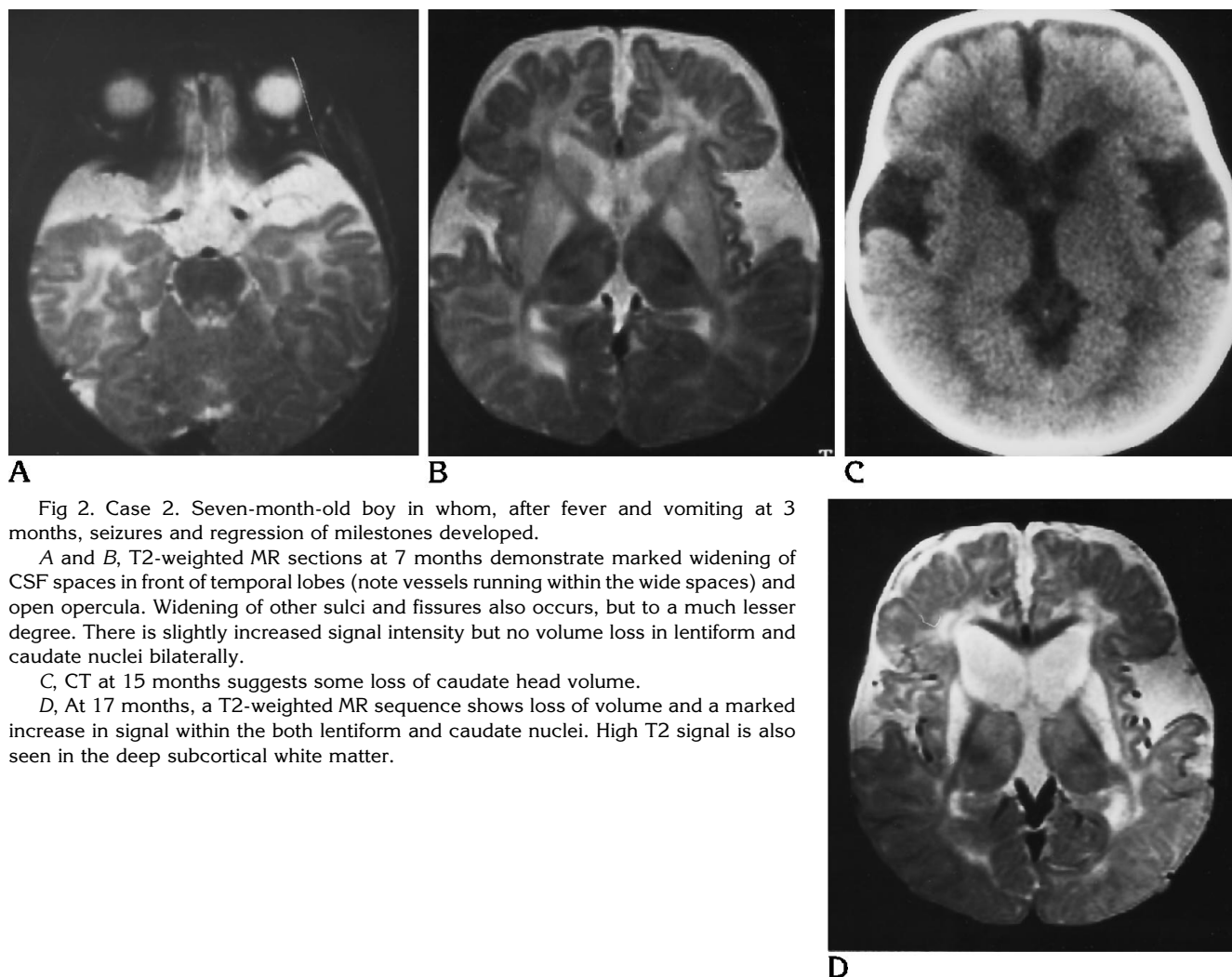


Fig 2. Case 2. Seven-month-old boy in whom, after fever and vomiting at 3 months, seizures and regression of milestones developed.

A and B, T2-weighted MR sections at 7 months demonstrate marked widening of CSF spaces in front of temporal lobes (note vessels running within the wide spaces) and open opercula. Widening of other sulci and fissures also occurs, but to a much lesser degree. There is slightly increased signal intensity but no volume loss in lentiform and caudate nuclei bilaterally.

C, CT at 15 months suggests some loss of caudate head volume.

D, At 17 months, a T2-weighted MR sequence shows loss of volume and a marked increase in signal within the both lentiform and caudate nuclei. High T2 signal is also seen in the deep subcortical white matter.

with preserved volume within both caudate heads and lentiform nuclei; volume loss of the caudate heads then follows, and later, necrosis also of the lentiform nuclei (Figs 2 and 3). MR is more sensitive than CT in depicting basal ganglia lesions, and basal ganglia involvement was noted in 9 (2, 16, 18, 22) of 14 patients (including our 5 patients), identifiable as examined with MR (12, 3, 13, 15–18, 22).

Table 2 relates the radiologic findings to the age at examination. Brain atrophy or hypoplasia was seen in two thirds of the patients in all age groups, white matter changes in half. Basal ganglia changes were less common below 1 year of age than later in life but were seen in half the patients older than 5 years of age. The extracerebral collections were most common between 1 and 5 years and in that age group were seen in 4 of 18 patients.

Clinically, the child with glutaric acidemia typically has a normal development during the first 4 to 15 months. Then, there is typically an acute onset of neurologic symptoms and signs, often after an infectious disease, sometimes after trauma. Sometimes the child is healthy until school age. In 42 of the 64 patients (including our 5 patients) reviewed, the mode of onset could be evaluated. In 7 the disease manifested as psychomotor delay; another 7 patients were found because of screening or a family history. In 28 the onset was acute, in 19 associated with infection, and in 2 associated with minor head trauma (20; our patient 3), whereas in 7 patients no predisposing factor was described.

During the acute episode, which was often clinically interpreted as encephalitis (3, 16), the child was usually severely ill, with decreased consciousness, dystonia, choreoathetosis, and

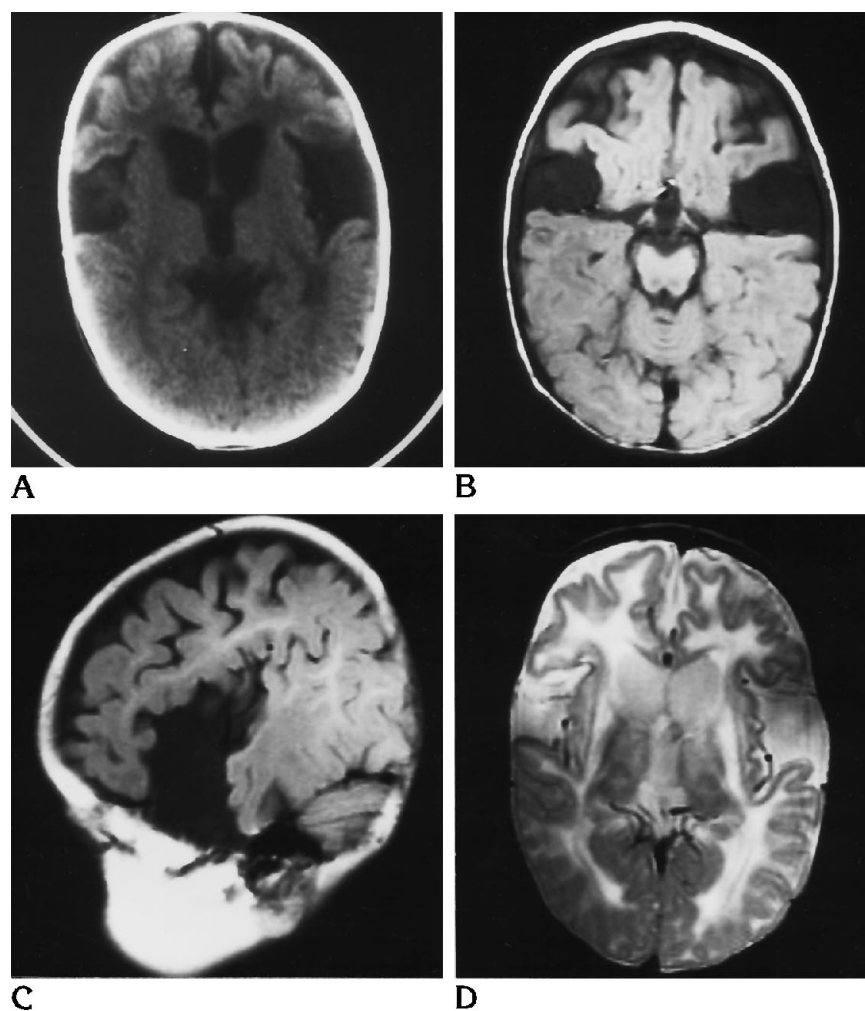


Fig 3. Case 3. Previously healthy 7-month-old boy, who the day after a head trauma presented with vomiting, diarrhea, and seizures and thereafter lost milestones and became dystonic with spastic quadriplegia.

A, CT at 7 months shows widening of the CSF spaces around the frontal lobes, underdevelopment of the temporal lobes with severe widening of the sylvian fissures, and wide open opercula. There is decreased white matter density within the frontal lobes and loss of caudate head volume.

B and C, At 10 months, T1-weighted axial and sagittal MR sections demonstrate the severe underdevelopment of the temporal lobes with wide CSF spaces anterior to the temporal lobes and within the sylvian fissures.

D, T2-weighted section from the same examination shows severe volume loss and high signal within the caudate heads and lentiform nuclei. There are severe generalized white matter changes.

seizures. The acute episode usually left the child severely dystonic, often with spastic quadriplegia and choreoathetosis. In 33 of the reported cases the degree of disability was addressed. Five patients died of the disease, 14 were severely and 3 moderately disabled, and 11 were

clinically normal or only slightly affected. One of these latter children, healthy at the last CT examination at 2.5 years, developed a Reye-like condition a half-year later after an infection, leaving her severely debilitated with dystonic quadriparesis (3).

TABLE 2: Brain CT and MR findings in glutaric aciduria type I in relation to the age of the patient

Age, y	Brain Atrophy or Hypoplasia	Wide Opercula	Dysmyelination, Demyelination	Basal Ganglia Lesions	Extracerebral Fluid Collections
<1*	10/14	11/13	7†/13	4/14	2‡/15
1–4*§	13/17	11 /12	9/16	8¶/17	4#/18
≥5§	4/9	9/9	5/9	5/10	1/10

* Four patients included in both groups.

§ One patient included in both groups.

† In two of those, only transient neonatal edema.

‡ One patient had collections at 10 months, none at 21 months.

|| In one child not seen at 6 weeks of age.

¶ Transient in two children.

One patient had collections at 1.5 years but not at 1 year or at 2.5 years.

Many of the organic acidemias may remain silent for many years and eventually present as a metabolic crisis after an infection, a condition that is not rarely misinterpreted as encephalitis. The same is true for Leigh disease, a disorder related to different defects of the enzyme systems related to energy metabolism. In these conditions, a CT or MR study in the acute stage may show brain swelling and low CT density, high T2-intensity lesions, with some swelling and possible contrast enhancement both in the basal ganglia and in the subcortical white matter. In later stages atrophy is often present, and white matter lesions and basal ganglia necrosis are frequently seen. Thus, both the clinical history and the findings of basal ganglia changes, white matter changes, and atrophy may occur in several different conditions. However, the characteristic widening of the opercula, prominent in glutaric acidemia type I, is rarely seen in other disorders. Especially when combined with basal ganglia lesions, this finding is almost pathognomonic for glutaric acidemia type I.

In 38 of the 64 patients the head size was commented on. In 30, macrocephaly was present, and several patients were referred for neuroradiologic evaluation of macrocephaly before neurologic findings had developed (13, 14). In one prospective study, children with macrocephaly during the first year of life were evaluated for organic acidemias (16); 1 child with asymptomatic glutaric acidemia type I was identified and could be treated. In another infant, investigation for macrocephaly led to the diagnosis of glutaric acidemia type I; this child was treated with diet and at 14 months had developed normally (13).

It is important that the radiologist involved in pediatric neuroradiology be aware that neuro-metabolic disorders may initially clinically manifest merely as macrocephaly. Macrocephaly may be the presenting symptom not only in glutaric acidemia type I, but also in Canavan disease (26), and may be a prominent feature in Alexander disease. In Canavan disease, one would expect to find prominent white matter changes, but not the marked prominence of the extracerebral CSF spaces almost always present in glutaric acidemia type I. In Alexander disease, CT at time of presentation almost invariably shows deep cerebral white matter low-density changes, typically most pronounced in the frontal lobes, and sometimes with enhance-

ment after administration of contrast medium (27). In Alexander disease, hydrocephalus may be seen, but widening of the extracerebral CSF spaces is not a feature.

Although the finding of wide opercula suggests glutaric acidemia type I, the finding is by no means specific. This sign may occur not only in association with severe developmental delay (28), but also in infants with idiopathic external hydrocephalus (29). This latter disorder may be a radiologically difficult differential diagnosis, in which head size is enlarged, and the extracerebral CSF spaces are unusually prominent (30); the white matter, however, is normal, and no basal ganglia changes are seen. The head growth in this condition slows at about 12 months of age and then parallels the normal curve, and the child, although previously delayed in psychomotor development, resumes normal development. The CSF collections normalize with time, as did the collections in two of our reviewed patients with glutaric acidemia type I. It seems entirely possible that some patients with idiopathic external hydrocephalus may in fact have had glutaric acidemia type I, because patients with this disease may reach adulthood without any clinical findings except macrocephaly.

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