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# Glutaric aciduria type 1 presenting as bilateral subdural hematomas mimicking nonaccidental trauma

## Case report and review of the literature

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✓Glutaric aciduria type 1 (GA1) is a rare neurometabolic disorder with characteristic neuroimaging and clinicopathological features. The authors describe a case of GA1 in a 7-month-old girl presenting with macrocephaly and bilateral subdural hematomas (SDHs) who was initially evaluated for nonaccidental trauma (NAT). Bilateral subdural drains were placed because of significant mass effect from the chronic SDHs, with subsequent neurological and neuroimaging-documented improvement. Clinical and neuroimaging findings led to further laboratory investigation to confirm the diagnosis of GA1, after which a specialized low-protein diet was initiated. After a thorough investigation, NAT was ruled out. At the follow-up examination, the patient experienced improvement in her symptoms and resolution of the bilateral subdural collections. The presence of bilateral SDHs in an infant raises the suspicion of NAT and presents a difficult diagnostic challenge because of the legal and social implications. Glutaric aciduria type 1 should be considered in the differential diagnosis of bilateral SDHs, and an evaluation should be performed. The authors review the clinical manifestations, diagnosis, medical and surgical management, and specific considerations regarding GA1, including misdiagnosis of NAT.

**Key Words** • **glutaric aciduria type 1** • **subdural hematoma** • **nonaccidental trauma** • **pediatric neurosurgery**

Glutaric aciduria type 1 is a rare neurometabolic disorder of lysine, hydroxylysine, and tryptophan metabolism caused by a deficiency in glutaryl-CoA dehydrogenase. This mitochondrial enzyme mediates oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA in the degradation pathway for lysine, hydroxylysine, and tryptophan. The accumulation of glutaric acids in GA1 can result in acute striatal necrosis, dystonic–dyskinetic disorder, hypotonia, and further neurological deterioration. Infants commonly present with macrocephaly and bilateral SDHs with or without retinal hemorrhages, which may be mistakenly diagnosed as NAT. The neuroimaging and clinicopathological features are unique for GA1. We describe a case of GA1 associated with bilateral SDHs in an infant who was initially thought to have sustained NAT. Glutaric aciduria type 1 was correctly diagnosed after a further laboratory investigation that was undertaken because of clinical and neuroimaging findings. Although GA1 is a rare condition, it should be considered in the differential diagnosis when a child presents with bilateral SDHs. We also review the literature on GA1 and discuss the clinical manifestations, diagnostic laboratory and neuroimaging findings, and medical and surgical management.

*Abbreviations used in this paper:* CT = computed tomography; GA1 = glutaric aciduria type 1; ICP = intracranial pressure; MR = magnetic resonance; NAT = nonaccidental trauma; SDH = subdural hematoma.

### Case Report

*History and Examination.* This 7-month-old girl initially presented to her pediatrician with macrocephaly. Her head circumference had increased from 44 to 48 cm over a 6-week period. A CT scan showed large bilateral chronic subdural collections causing moderate underlying mass effect (Fig. 1). The fluid density was mildly increased in comparison with that of cerebrospinal fluid, suggesting chronic SDHs. The pediatrician suspected NAT and admitted the patient to Primary Children's Medical Center for treatment and evaluation to rule out NAT. The patient had not had any previous medical illnesses, and her birth was uneventful. The mother denied any recent history of head trauma.

On examination, the child was macrocephalic and had a

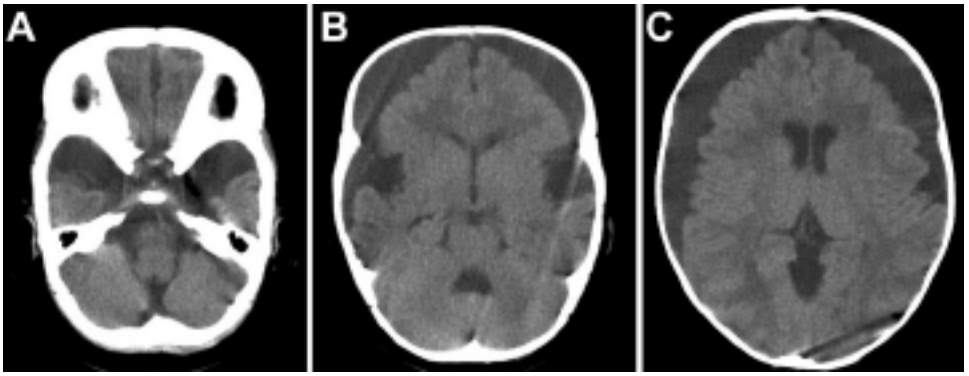


FIG. 1. Computed tomography scans demonstrating subdural collections in the middle cranial fossa (A), bilateral prominent opercular cisterns (B), and large bilateral chronic SDHs (C) causing moderate underlying mass effect.

soft anterior fontanelle. There was no evidence of external trauma. The patient was awake, behaving appropriately for her age, and moving all extremities. Cranial nerve and sensory examinations were grossly normal. Motor examination revealed adequate muscle bulk and strength, and mild, diffuse muscular hypotonia. Her deep tendon reflexes were normoactive and symmetrical. In recent months, she had exhibited mild developmental delay in meeting her milestones.

Because of the initial clinical presentation, NAT was suspected and the investigative protocol was initiated by the Department of Children and Family Services, and the Safe and Healthy Families team. A formal retinal examination did not reveal retinal hemorrhages, and the skeletal survey revealed no fractures. Magnetic resonance imaging of the brain revealed large supratentorial frontotemporoparietal subdural collections that were hypointense on $T_1$-weighted imaging and hyperintense on $T_2$-weighted imaging. The opercular cisterns were also prominent bilaterally in a batwing configuration (Fig. 2). On $T_2$-weighted imaging, there was increased signal within the globus pallidus bilaterally, with diffusion restriction in the bilateral globus pallidus,

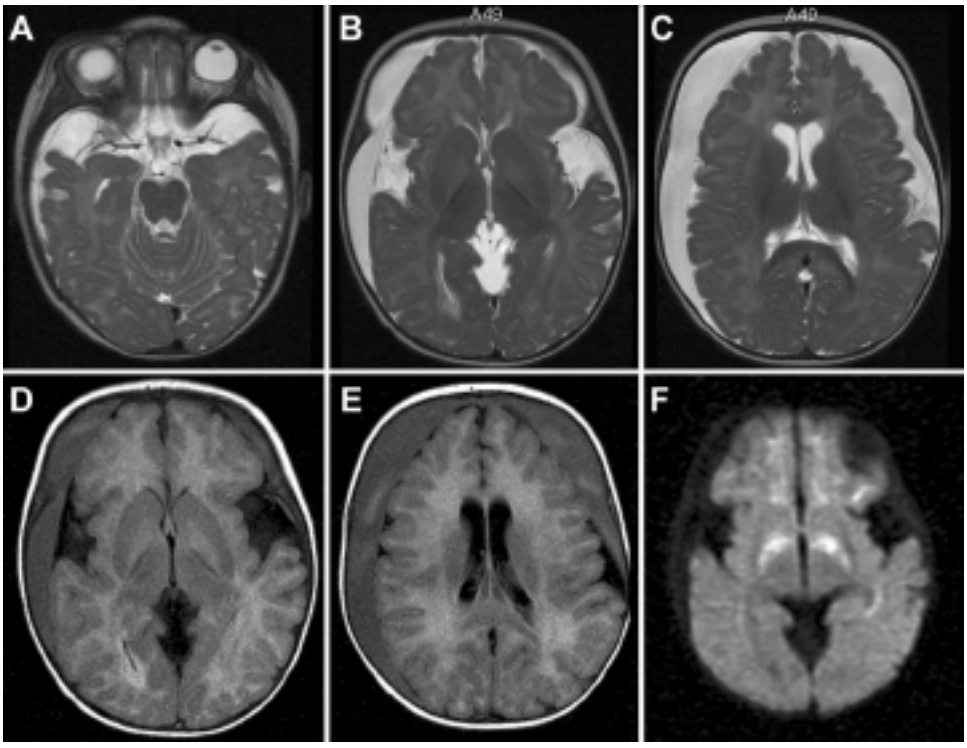


FIG. 2. Axial MR images of the brain. A–C: A series of $T_2$-weighted images demonstrating subdural collections in the middle cranial fossa (A), bilateral prominent opercular cisterns (B), and large bilateral chronic subdural collections (C) causing moderate underlying mass effect. D and E: Two $T_1$-weighted images showing bilateral chronic SDHs. The opercular cisterns remain prominent with cerebrospinal fluid (D). F: A diffusion weighted image demonstrating diffusion restriction in the bilateral globus pallidus and frontal white matter. These unifying features of bilateral subdural collections, batwing opercular cisterns, abnormal signal intensity within the globus pallidus, and patchy white matter signal abnormalities support the diagnosis of GA1.

dorsal pons, upper brainstem, hippocampi, and frontal white matter on diffusion weighted imaging. The unifying features of batwing opercular cisterns, abnormal signal intensity within the globus pallidus, and patchy white matter signal abnormalities suggested the diagnosis of GA1. After a thorough investigation, the diagnosis of NAT was ruled out.

*Treatment.* Because of significant mass effect from the chronic SDHs, the patient underwent placement of bilateral subdural drains. At surgery, blood-tinged fluid returned briskly under moderate pressure. The subdural drains were removed after 48 hours without complication. The patient demonstrated mild to moderate neurological improvement, and the subdural collections appeared decreased on postoperative imaging.

Further investigation with laboratory studies confirmed the diagnosis of GA1. Screening of urine organic acids revealed excess levels of glutaric acid and 3-hydroxyglutaric acid. Plasma carnitine levels were low. An enzymatic assay of cultured fibroblasts demonstrated glutaryl-CoA dehydrogenase deficiency. The clinical, neuroimaging, and laboratory findings were diagnostic of GA1.

The patient was started on a special low-protein diet, comprising Glutarex-1 (Ross Products), formula with iron, and Pro-Phree (Ross Products), which was supplemented with intravenous carnitine to prevent the accumulation of glutaric acid. The patient tolerated enteral feedings, and the mother was counseled on the importance of dietary restriction. The patient was discharged on postoperative Day 6.

*Posttreatment Course.* Overall, the patient has had significant improvement. At her 11-month follow-up visit, her head circumference measurement of 51 cm was still above the 95th percentile for age, but her growth curve was tracking in parallel with the normal upper end of the curve. Her head control and hypotonia were greatly improved, and she was meeting developmental milestones. A follow-up CT scan obtained 11 months postoperatively demonstrated resolution of the subdural collections (Fig. 3). There was persistent prominent extraaxial fluid in both sylvian fissures. On follow-up laboratory testing, urine glutaric acids levels were low, consistent with good dietary control.

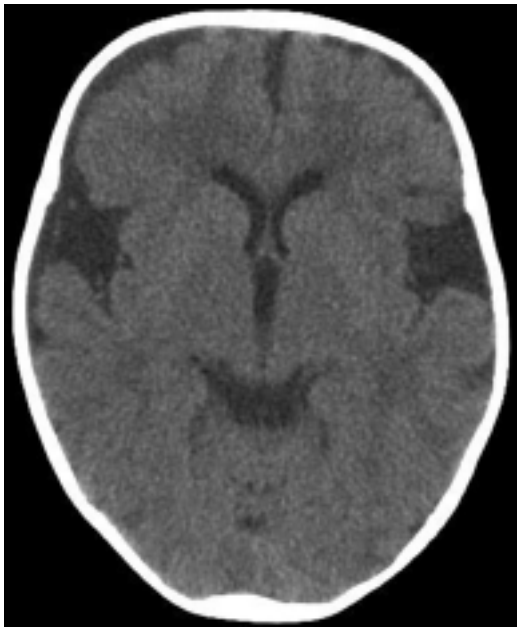

FIG. 3. Postoperative CT scan obtained at the 11-month follow-up examination, demonstrating resolution of the subdural collections. There is persistent prominent extraaxial fluid in both sylvian fissures.

## Discussion

Glutaric aciduria type 1 is an autosomal-recessive disorder resulting from a deficiency of mitochondrial glutaryl-CoA dehydrogenase,[3] which is involved in the metabolism of lysine, hydroxylysine, and tryptophan. The accumulation of glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid results in metabolic abnormalities ranging from slightly or intermittently elevated urinary glutaric acid to gross organic aciduria.[7] This disease has been estimated to occur in one of 30,000 neonates.[9]

### *Clinical Manifestation*

The clinical presentation of patients with GA1 varies considerably.[7] At birth, macrocephaly may occur, sometimes manifesting with major neurodevelopmental malformations. In infancy, the initial clinical manifestation of GA1 is often relatively mild, presenting as hypotonia, feeding difficulties, and irritability. Other patients are asymptomatic until the 2nd year of life. As in the present case, an enlarged head circumference may be the only presenting sign in many neonates with GA1.

The mild clinical manifestations usually go unnoticed until patients present with an acute encephalopathic crisis. These episodes are characterized by an acute neurological deterioration, manifesting as loss of motor skills and dystonia, and translating clinically to hypotonia of the neck and trunk with loss of head control, decreased suck and swallow reflexes, and the inability to sit or stand. The episodes may be accompanied by development of a dystonic–dyskinetic movement disorder that is often mistaken for cerebral palsy. Generalized seizures may also occur in approximately 20% of patients.[5]

These encephalopathic crises are thought to be due to metabolic derangement during states of increased catabolism from physiological stress. They frequently occur in conjunction with febrile illnesses (most commonly upper respiratory and/or gastrointestinal infection), after routine immunizations, after minor head injuries, or after fasting in preparation for surgery. They have also been reported after neurosurgical intervention when the patient is in a state of general anesthesia.[6,7,10] Recovery occurs slowly, usually with persistence of some neurological abnormalities.

Permanent disability is caused by selective damage to the basal ganglia (acute striatal necrosis), which typically begins between 6 and 18 months of age.[7] Although intellectual ability remains relatively normal, the chronic course is characterized by progressive white matter and midbrain involvement over several years, ranging clinically from hypotonia to choreoathetosis to rigidity with spasticity. If GA1 remains undiagnosed, cerebral atrophy with pyramidal tract signs and mental retardation may develop. Disease progression ends in later childhood or adulthood. Each additional encephalopathic episode may cause further neurolog-

ical disability, the most serious sequelae being disturbances in feeding and body temperature regulation, mainly hyperpyrexia. The degree of neurological disease, the nutritional status of the patient, and the interdisciplinary care provided are important factors in determining the final neurological outcome of the patient.[6,7]

*Diagnostic Laboratory and Neuroimaging Findings*

Diagnosis consists of clinical, biochemical, and neuroimaging evaluation for features consistent with GA1. Biochemical analysis consists of urinary organic acid and serum carnitine testing. Urinary glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and glutarylcarnitine are elevated, and plasma carnitine is reduced indicating a diagnosis of GA1. More definitive evidence can be provided by enzymatic assays of cultured fibroblasts or interleukin-2-dependent cultured lymphocytes that reveal diminished activity of glutaryl-CoA dehydrogenase.[5,9] Persistent testing may be necessary as some patients have only slightly or intermittently elevated urinary glutaric acid excretion. In molecular studies authors have demonstrated a wide variety of mutations in the *glutaryl-CoA dehydrogenase* gene that are responsible for the disease.[16]

The neuroimaging manifestations of GA1 are characteristic. Microencephalic macrocephaly is a distinctive neuroimaging feature of GA1. Magnetic resonance or CT imaging typically reveals frontotemporal cerebral atrophy with resultant widening of the sylvian fissures and subdural and subarachnoid spaces. These expanded opercular cisterns have been mistaken as bilateral temporal arachnoid cysts, although true bilateral arachnoid cysts have been reported in patients with GA1.[8,10] Delayed myelination may be present and is characterized by diffuse white matter signal hyperintensity on $T_2$-weighted MR imaging.[5,6,8,11,19] These findings may precede the clinical manifestation of GA1. Progressive hydrocephalus, shrinkage of the putamen and lateral caudate with "straightening" of the internal capsule, and transient subependymal pseudocysts have also been described. Diffusion weighted imaging may reveal diffusion restriction of the bilateral putamen, globus pallidi, and caudate nuclei, consistent with acute striatal necrosis.[1]

Acute and chronic SDHs and effusions are also common neuroimaging findings in GA1[4,13,18] and have been reported to be present in 20 to 30% of patients.[6] The development of both subdural and retinal hemorrhages[2,7] may follow relatively mild head trauma, which commonly occurs around the first birthday when the child begins to walk. These findings usually prompt an investigation for NAT, which may delay the diagnosis of GA1. It has been postulated that the prominence of the subarachnoid and subdural spaces in GA1 results in elongated and stretched veins from cerebral atrophy, predisposing patients with GA1 to SDHs and retinal hemorrhages after minor trauma.[14,17]

*Medical and Surgical Management*

Medical management of GA1 consists primarily of dietary modification with a high-calorie, low-protein diet. Patients are placed on special formulations low in lysine and tryptophan, with carnitine and riboflavin supplementation. Although the long-term benefits are yet to be determined, immediate institution of diet therapy after diagnosis is generally recommended.[6,7] Aggressive treatment to prevent or minimize acute encephalopathic crises is of extreme importance and consists of emergency treatment of intercurrent illnesses, fever reduction, early electrolyte and glucose infusions, and carnitine supplementation. The primary goal of early and aggressive treatment in symptomatic patients is the prevention of further neurological deterioration, and some reports suggest that patients who have not yet developed symptoms may benefit from slowing the onset of disease.[6,7]

Little has been reported regarding the surgical treatment of GA1. Neurosurgical intervention may be warranted if associated lesions such as subdural collections and arachnoid cysts exert mass effect on the brain resulting in neurological deterioration. In our case, the patient exhibited excellent neurological and neuroimaging-documented outcomes after drainage of her bilateral subdural collections. Other authors have reported improved neurological outcome after cystoperitoneal shunt treatment of large arachnoid cysts.[8]

Although we and other authors have reported good outcomes after surgery, general anesthesia and neurosurgical interventions should be considered with caution and only after complete evaluation and preoperative optimization have been performed, as marked postoperative neurological deterioration has also been reported. This decline is thought to be due to the stress of surgery and anesthesia inducing a catabolic state, resulting in a process similar to an acute encephalopathic crisis causing production of harmful metabolites and subsequent neurological worsening.[10] Surgery should be considered only when strictly essential, that is, when there is considerable mass effect or increased ICP. In ambiguous cases, patients should be evaluated before surgery for evidence of increased ICP by using clinical evaluation, serial imaging, or measurement of ICP if necessary. Intercurrent illnesses should be evaluated and treated before surgery when possible, and patients should be optimized medically and nutritionally in an attempt to prevent a postoperative encephalopathic crisis. The possibility of neurological decline after surgery should be discussed with patient families. Alternatively, treatment after administration of a local anesthetic (for example, bedside drainage of subdural fluid) may be considered. Severe dystonia in patients with GA1 can be difficult to manage medically. There is one report of bilateral pallidotomy performed in an infant with GA1 that improved severe pain and dystonic symptoms.[15]

*Glutaric Acid Type 1 Mimicking NAT*

Our case demonstrates the diagnostic challenge of ruling out NAT in a patient with undiagnosed GA1. The presence of bilateral SDHs of varying ages, retinal hemorrhages, and nonspecific symptoms may lead physicians to presume NAT has occurred in a patient with undiagnosed GA1.[2,4] The grave legal and social consequences resulting from the diagnosis of NAT place the responsibility on the physician to definitively eliminate alternative diagnoses. Physicians should be familiar with the clinical and neuroimaging features of GA1, and screening for GA1 should be added to the evaluation of NAT, especially in atypical or ambiguous cases.[4] However, children with neurometabolic disorders are at increased risk for NAT, and therefore concerns regarding a child's safety and protection should not end with the diagnosis of GA1.[12]

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