


Severe Acute Subdural Hemorrhage in a Patient With Glutaric Aciduria Type I After Minor Head Trauma: A Case Report

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Matthias Zielonka, MD¹, Katrin Braun, MD², Andreas Bengel, MD³,
Angelika Seitz, MD⁴, Stefan Kölker, MD¹, and Nikolas Boy, MD¹

Abstract

Glutaric aciduria type I is a rare metabolic disorder caused by deficiency of glutaryl-coenzyme A dehydrogenase. Chronic subdural hematomas have been reported in glutaric aciduria type I and are considered as important differential diagnosis of nonaccidental head trauma. However, chronic subdural hematomas are usually thought to remain clinically silent in these patients. Here we report on a hitherto asymptomatic glutaric aciduria type I patient who developed severe, acute subdural hemorrhage after minor accidental head injury at age 23 months. Computed tomography confirmed significant mass effect on the brain necessitating decompressive hemicraniectomy. Subdural hemorrhage caused large hypoxic lesions of the cerebral cortex and subcortical regions resulting in spastic tetraplegia, dystonia, and loss of developmental milestones. This report emphasizes that acute subdural hemorrhage may be a life-threatening complication in glutaric aciduria type I patients after minor head trauma and should be considered in those patients presenting with neurologic deterioration after accidental head injury.

Keywords

glutaric aciduria type I, acute subdural hemorrhage, minor accidental head trauma, tetraspasticity, hemicraniectomy

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Glutaric aciduria type I is an autosomal recessively inherited metabolic disorder with an estimated prevalence of about 1:100 000 newborns.¹ The molecular basis is inherited deficiency of glutaryl-coenzyme A dehydrogenase (GCDH; EC 1.3.99.7) which is caused by 2 disease-causing mutations in the *GCDH* gene on 19p13.2. So far more than 200 mutations have been identified.^{2,3} GCDH is a mitochondrial homotetrameric flavoprotein that catalyzes the oxidative decarboxylation of glutaryl-coenzyme A (CoA) to crotonyl-CoA in the final degradative pathway of amino acids L-lysine, L-hydroxylysine, and L-tryptophan. GCDH deficiency leads to increased formation of glutaryl-CoA, glutaric acid, 3-hydroxyglutaric acid, and glutarylcarnitine. As the blood-brain barrier does not have a specific transporter system for dicarboxylic acids, these dicarboxylic metabolites are thought to be trapped in the brain.^{4,5} This forms the basis of a metabolite-induced neurotoxic mechanism affecting glutamatergic signaling, brain energy metabolism, and cerebral hemodynamics.⁶⁻⁸ Untreated patients have an increased risk of developing a complex movement disorder with predominant dystonia due to striatal injury.⁹ Metabolic treatment is based on a low lysine diet and supplementation of carnitine in combination with metabolic emergency treatment during episodes that are likely to induce catabolism. This therapeutic strategy prevents the manifestation of striatal injury in the majority of

patients identified by newborn screening^{1,8,10} and thus has been recommended in a recent guideline.¹¹

Besides striatal injury, magnetic resonance imaging (MRI) studies have elucidated a number of extrastriatal abnormalities that are usually not associated with a clear-cut clinical presentation or even remain clinically silent.^{12,13} These magnetic resonance imaging abnormalities include widening of anterior temporal and sylvian cerebrospinal fluid spaces, pseudocysts, signal changes of substantia nigra, nucleus dentatus, thalamus, tractus tegmentalis centralis and supratentorial white matter, and signs of delayed maturation.^{12,14,15} In addition, acute and, more

¹ Division of Inherited Metabolic Diseases, Department of General Pediatrics, University Hospital Heidelberg, Heidelberg, Germany

² Department of General Pediatrics, Children's Hospital Ludwigsburg, Ludwigsburg, Germany

³ Institute for Diagnostic and Interventional Neuroradiology, Hospital Ludwigsburg, Ludwigsburg, Germany

⁴ Division of Neuroradiology, Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany

Corresponding Author:

Nikolas Boy, MD, Department of General Pediatrics, Division of Inherited Metabolic Diseases, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany.
Email: nikolas.boy@med.uni-heidelberg.de

frequently, chronic subdural hematomas have been described in glutaric aciduria type I.^{12,15-17} Although subdural hematomas have been reported at a higher frequency (20%-30%) in previous studies,¹⁸ subdural hematomas are less frequently found in more recent studies,¹² suggesting a positive effect of newborn screening and early start of treatment. A life-threatening acute subdural hemorrhage in an early diagnosed and treated individual with glutaric aciduria type I has not been described yet. Here we report on a patient with glutaric aciduria type I who developed a severe acute subdural hemorrhage after minor accidental head trauma.

Case Summary

History and Examination

The girl was identified by newborn screening at age 5 days (glutaryl-carnitine in dried blood spots 5.57 $\mu\text{mol/L}$, cut-off <0.35 $\mu\text{mol/L}$) and suspected diagnosis of GA-I was subsequently confirmed by elevated urinary concentrations of glutaric acid (6674 mmol/mol creatinine, normal range <10 mmol/mol creatinine) and 3-hydroxyglutaric acid (117 mmol/mol creatinine, normal range <8 mmol/mol creatinine) and homozygosity for the known missense-mutation p.Arg402Trp (c.1204C>T) in the *GCDH* gene. At the time point of diagnosis, she was asymptomatic and had a normal head circumference. Combined metabolic treatment consisting of low lysine diet and carnitine supplementation (100 mg/kg/d) was immediately started. Motor and mental development has been considered as appropriate for age until age 23 months. Head growth was stable along the 75th percentile. Clinically there was no evidence for an underlying thrombopathy, plasmatic coagulopathy, or intracranial vascular malformation. The girl was admitted to hospital after accidental head trauma at age 23 months. She had fallen from a drop height of 50 cm and had dashed against the carpeted floor with her head. Loss of consciousness or focal neurologic defects were not reported by the parents but soon after the infant started recurrent vomiting. On admission, she did not reveal any neurologic abnormalities. A slight frontal subcutaneous hematoma was noted. She was admitted to the general pediatric ward for further supervision of vital parameters and clinical evaluation, which did not show any abnormal neurologic findings. Sporadic vomiting was observed (once a day) initially but stopped within 48 hours after admission. Metabolic emergency treatment was not administered because of spontaneous regression of symptoms. The patient was discharged after 48 hours in good general condition. Only a few hours after she had returned home, she presented with a generalized seizure and lost consciousness. On readmission to hospital, the girl was comatose and exhibited signs of elevated intracranial pressure with anisocoria and reduced pupillary reflexes to light. Respiratory insufficiency necessitated orotracheal intubation. Emergency cranial computed tomographic scan showed severe acute subdural hemorrhage at the left brain convexity, with surrounding brain edema causing subsequent mass effect with midline shift and obliteration of the bilateral ventricular

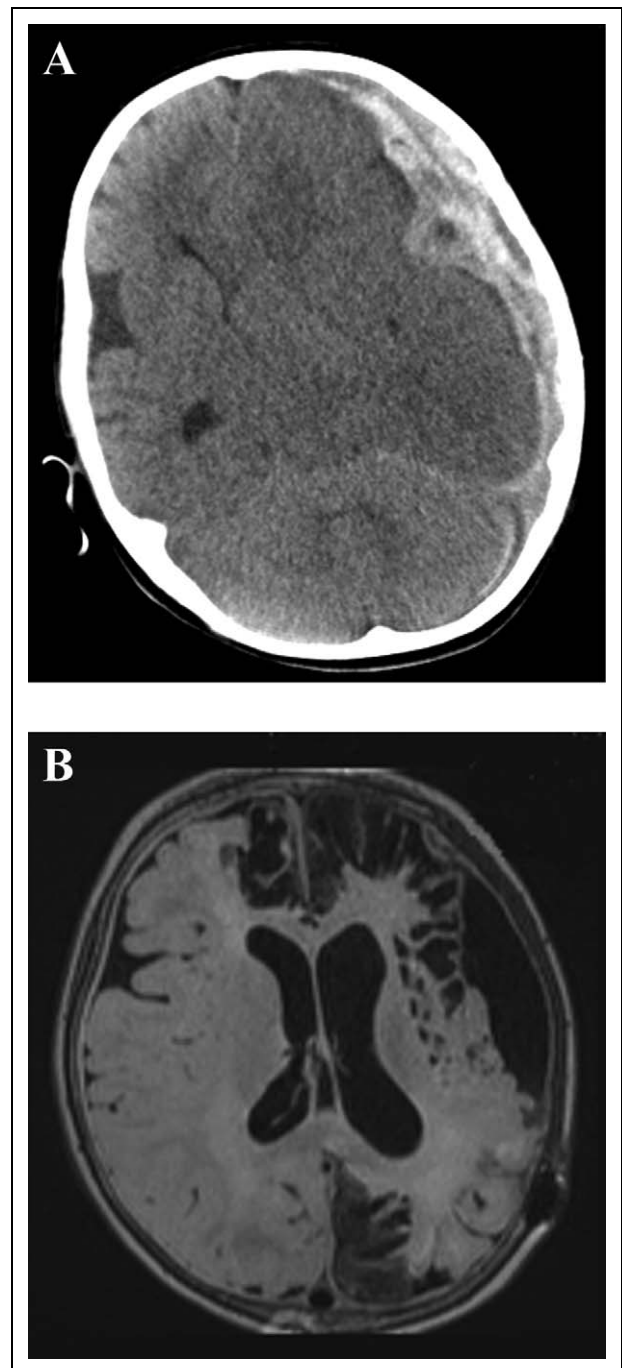


Figure 1. (A) Computed tomographic scan showing large subdural hemorrhage causing significant underlying mass effect with complete collapse of the bilateral second ventricles. Note absence of enlargement of the subdural spaces. (B) Magnetic resonance imaging (MRI) scan 6 months after surgery demonstrating dilated ventricles on both sides with resolution of the subdural hemorrhage. Severe hypoxia induced the development of a multicystic encephalomalacia pronounced on the left hemisphere with persistent subdural effusions.

system. Of note, clear enlargement of external cerebrospinal fluid spaces as a typical morphological presentation of GA-I was absent (Figure 1A).

Treatment

Metabolic emergency treatment with intravenous glucose infusion (10 g/kg/d) and L-carnitine supplementation (100 mg/kg/d) was started immediately. Because of significant elevation of intracranial pressure, the patient underwent an emergent left-sided decompressive hemicraniectomy with implantation of an intracranial pressure sensor. The neurosurgical intervention was complicated by thrombopenia (thrombocytes 16/nL) and transient coagulopathy (INR 1.83) necessitating multiple transfusions of thrombocytes and fresh-frozen plasma. Postsurgical monitoring was unremarkable. In particular, she did not present with significant elevation in intracranial pressure (mean intracranial pressure (mmHg) 7.1, median 7, minimum 0, maximum 25). However, anisocoria persisted and the left pupil did not react to light. To evaluate the result of the hemicraniectomy, a cranial computed tomographic scan was performed on the first day after surgery confirming the partial removal of the acute subdural hemorrhage. Despite this, hypodensity of the left dorsal lobe and the left basal ganglia region was noted indicating hypoxic damage secondary to increased cranial pressure. Cranial magnetic resonance imaging confirmed massive hypoxic lesions involving the left hemisphere expanding to deeper structures such as the basal ganglia. After extubation at day 10 after surgery, the girl showed spastic tetraparesis with predominance of the right side, which was also accompanied by asymmetric bilateral dystonia, anarthria, and severe axial muscular hypotonia. The deep tendon reflexes were hyperactive with widened reflex zones. She developed bilateral pes equinus. Her severe movement disorder was improved by physical therapy. Anticonvulsive treatment with phenobarbital (5mg/kg body weight/d) was started after extubation and maintained for a total of 125 days with subsequent dosage reduction.

Because of recurrent subdural hematomas over the left hemisphere, cerebrospinal fluid punctures were repeatedly performed. On day 29 after neurosurgical intervention, the patient underwent implantation of a ventriculoperitoneal shunt (ProGAV™-valve with shunt assistance 4 cm H₂O) because of the manifestation of posthemorrhagic hydrocephalus. Nutrition was administered via nasogastric tube and switched to her normal dietary treatment protocol (1 g protein/kg body weight/d, 70 mg lysine /kg body weight/d) with a total energy intake of 80 kcal/kg body weight/d. Thirty-eight days after hemicraniectomy, the patient was discharged for neurologic rehabilitation.

Postoperative Neurologic Course

In the following 3 months, the girl received neurologic rehabilitation with occupational, speech, and physical therapy and partially recovered from brain damage following acute subdural hemorrhage. Six months later, anisocoria had completely resolved and spastic tetraparesis had improved significantly. Muscle strength was normal with symmetric, hyperactive deep tendon reflexes in the lower extremities and widened reflex zones. However, the patient still showed persistent axial hypotonia, and head control was reduced. In addition, she learned

again to articulate approximately 20 words, but still needed nasogastric tube feeding because of orofacial dyskinesia with impaired swallowing. No further seizures were noted after termination of anticonvulsive treatment. A follow-up cranial magnetic resonance imaging scan at 6 months after surgery demonstrated pronounced multicystic encephalomalacia on the left hemisphere due to severe hypoxic lesions (Figure 1B). Follow-up laboratory testing was unremarkable. Essential nutrients and micronutrients were adequately supplied, and dietary treatment was administered according to the guideline.¹¹

Discussion

Acute subdural hemorrhages are rarely found in infancy and are associated with significant neurodisability in affected individuals. Estimated incidence is between 12 and 25 cases per 100 000 infants.¹⁹⁻²¹ In the infant brain, acute subdural hemorrhages are caused by tearing of bridging veins in the subdural space due to rotational and decelerating forces and may lead to severe brain injury. For glutaric aciduria type I, it has been hypothesized that microencephalopathic macrocephaly with subsequently expanded external cerebrospinal fluid spaces increases the risk of stretching bridging veins and thus subdural hemorrhage, which may occur after minor accidental head trauma or even spontaneously.²² Macrocephaly is present in approximately 70% of both symptomatic and asymptomatic GA-I patients.⁹ In our case, acute life-threatening subdural hemorrhage occurred after minor head injury at age 23 months in a thitherto clinically asymptomatic infant. Despite emergency neurosurgical decompression, hypoxic lesions of the cortex and deeper structures occurred, resulting in a severe complex movement disorder. Hypoxic lesions of cortex and basal ganglia region were asymmetric and mainly localized on the left side involving putamen, globus pallidus, and nucleus caudatus to the same extent. As encephalopathic crises in glutaric aciduria type I regularly leads to a *symmetric* damage of basal ganglia with signal intensity changes mainly in the posterolateral putamina,^{12,14} magnetic resonance imaging findings in our patient are most likely caused by acute subdural hemorrhage and not by the manifestation of an encephalopathic crisis. In contrast to the “classical” clinical presentation with macrocephaly, our patient did not present with microencephalic macrocephaly, suggesting alternative mechanisms that can lead to vascular vulnerability. Recent evidence revealed that cerebral toxicity caused by GCDH deficiency might induce arteriolar dilation with decreased arterial velocity and elevated cerebral blood volume, especially between age 13 and 24 months. This might lead to altered autoregulation, disturbed perfusion pressure, and cerebral venous hypertension, with subsequently increased hemorrhage risk.²³ Because these events have been shown not only to contribute to cerebrospinal fluid space expansion but to be also present in GA-I patients with a normal size of subdural spaces, increased cerebral venous hypertension might be the main mechanism causing subdural hemorrhage in GA-I patients in the absence of microencephalic

macrocephaly. Rapid clinical assessment and early neuroimaging in any patient suspected for elevated intracranial pressure is essential to confirm the diagnosis of subdural hemorrhage as early as possible. Signs of increased intracranial pressure (ie, papilledema, repeated vomiting, pathologic pupil reaction, Glasgow Coma Scale score <8, prominent fontanel) might not be present in the clinical examination although intracranial pressure is already elevated. In more than 25% of patients with subdural hemorrhage, diagnosis is delayed for more than 1 week after admission because of non-specificity of presented symptoms²⁰ (ie, drowsiness irritability, pallor, floppiness). This highlights the importance of neuroimaging that should be rapidly performed with any clinical suspicion of subdural hemorrhage, especially in glutaric aciduria type I patients with microencephalic macrocephaly but also in those patients with a normal head circumference due to altered cerebral hemodynamics with increased vascular vulnerability. Subdural hemorrhage should always be considered as a possible cause in any unwell glutaric aciduria type I patient after minor head trauma even if macrocephaly or a clear enlargement of the subdural spaces is absent. While skull fractures can easily be diagnosed via computed tomographic scans, magnetic resonance imaging should be the favorable diagnostic method as it sensitively identifies even small subdural hemorrhages that cannot be discovered by cranial computed tomographic scans. Neurosurgical interventions have been debated controversially because stress during and after surgery causes catabolism with formation of harmful metabolites if metabolic emergency treatment is not administered. This can lead to subsequent neurologic worsening after surgery, which mainly has been reported in patients with undiagnosed glutaric aciduria type I.²⁴ In case of subdural collections exerting significant mass effect on the brain emergent neurosurgical interventions (subdural drainage, hemicraniotomy, etc) are indispensable to prevent further neurologic impairment. In our case the patient exhibited significant amelioration after decompressive hemicraniotomy. Unfortunately, a restitutio ad integrum was not observed. The hypothetic possibility that residual neurologic deterioration might be partially due to the relatively late implantation of ventriculoperitoneal shunt at day 29 cannot be excluded.

Conclusion

The presented case highlights that acute subdural hemorrhage is a major life-threatening complication in glutaric aciduria type I patients even in the absence of an enlargement of subdural spaces and therefore should be considered in any unwell GA-I patient as important differential diagnosis after minor accidental head injury.

Author Contributions

MZ is responsible for conception and drafting of the manuscript and provided clinical care to the patient. NB provided clinical care to the patient and prepared the manuscript as senior author. KB and SK provided clinical care to the patient (attendings). AB and AS are

responsible for radiologic data acquisition and interpretation. All authors contributed to the critical revision of the manuscript for intellectual content and gave final approval for the version to be published.

Declaration of Conflicting Interests

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Ethical Approval

No approval from the institutional review board was necessary as this is a case report without inclusion of any identifying information. Informed consent was obtained by the parents prior to drafting the manuscript.

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