Reversibility of Severe Cerebral Magnetic Resonance Imaging Changes Associated with Ethylene Glycol Toxicity

Erin B. Owen¹ Aaron W. Calhoun¹ Mark J. McDonald¹

¹Division of Critical Care Medicine, Department of Pediatrics, University of Louisville, Louisville, Kentucky, United States

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Address for correspondence Erin B. Owen, MD, Division of Critical Care Medicine, Department of Pediatrics, University of Louisville, 571 S. Floyd, STE 332, Louisville, KY 40202, United States (e-mail: erin.owen@louisville.edu).

Abstract

Keywords

- ▶ ethylene glycol toxicity
- ▶ magnetic resonance imaging
- ▶ computed tomography
- ▶ cerebral edema

Ethylene glycol (EG), commonly found in antifreeze and deicing solutions, continues to be a cause of morbidity and mortality in the pediatric population. EG metabolism produces toxins that cause metabolic acidosis and calcium oxalate deposition throughout the body. Deposition in the central nervous system is associated with significant neurologic sequelae, including altered mental status, seizures, and cerebral edema. We present a case of intentional EG poisoning in a 17-year-old male with resulting cerebral edema and coma. Neuroimaging studies were initially normal but eventually demonstrated diffuse abnormalities on both cranial computed tomography and magnetic resonance imaging (MRI). The patient ultimately made a complete recovery with resolution of the MRI abnormalities noted at the peak of illness. While neuroimaging is often incorporated into the management of EG poisoning, this is the first case report to show the evolution of EG-related MRI changes before, during, and after the resolution of EG-induced intracranial hypertension.

Introduction

Ethylene glycol (EG) is a sweet tasting alcohol that continues to remain a cause of morbidity and mortality in the pediatric age group. Approximately 1,100 pediatric exposures (with no fatalities) were reported to poison centers in 2014 alone.¹ EG is most commonly found in antifreeze and deicing solutions. Animal studies have suggested a minimum lethal dose of 1 to 1.5 mL/kg, although patients ingesting over 1 L have survived with immediate treatment. EG is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase leading to production of toxic metabolites including glycolaldehyde, glycolic acid, glyoxylic acid, and oxalic acid.² Of these, the toxins of most clinical significance are glycolic acid, which causes metabolic acidosis, and oxalic acid, which readily binds to soluble calcium and subsequently precipitates as calcium oxalate crystals. Deposition of these crystals can occur throughout the body, but most frequently occurs in the

kidney, brain, liver, lungs, and spleen.^{2–10} The following case report describes successful management of a young man following intentional EG poisoning who developed significant neurologic sequelae. Serial cranial neuroimaging was used to guide therapy. This case report is the first to show serial magnetic resonance imaging (MRI) findings after EG ingestion depicting the evolution and resolution of EG-associated brain pathology.

Case Presentation

A 17-year-old healthy male presented to our pediatric intensive care unit (PICU) after ingesting an unknown quantity of EG. Approximately 2 days prior to admission, he complained of headache and emesis. One day prior to admission he was disoriented with an ataxic gait and diplopia. A cranial computed tomography (CT) scan performed at an outlying hospital was read as normal. The next morning his disorientation

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Fig. 1 Magnetic resonance imaging images from day of admission, demonstrating normal brain. (A) T2-weighted image of the basal ganglia. (B) Fluid attenuated inversion recovery (FLAIR) sense image of the basal ganglia. (C) Diffusion-weighted image (DWI) of the basal ganglia. (D) T2-weighted image of the cerebellum. (E) FLAIR sense image of the cerebellum. (F) DWI cerebellum.

and confusion worsened, and he presented to our emergency department where he was noted to have a positive Romberg's test, finger-to-nose dysmetria, and diminished muscle strength. A brain MRI was performed and showed no pathology (►Fig. 1A–F). The patient was intubated due to neurologic deterioration (combative with Glasgow Coma Score 10) and transferred to the PICU (►Table 1).

Upon arrival to the PICU, he was deeply comatose with no response to painful stimuli, but pupils were reactive and equal. Vital signs exhibited tachycardia (115–140 beats per minute) and hypertension (220/104 mm Hg). He otherwise had an unremarkable cardiovascular, respiratory, abdominal, and skin examination. Initial laboratory studies demonstrated profound anion and osmolar gap acidosis (pH 6.96), evolving kidney injury (Blood urea nitrogen 15 mg/dL and Creatinine 1.3 mg/dL), and an EG level of 179 mg/dL. Initial treatment included hemodialysis, fomepizole, and labetalol.

On hospital day 1, generalized tonic-clonic seizures developed, prompting a cranial CT scan revealing effacement of cerebral sulci and extra-axial cerebral spinal fluid space consistent with cerebral edema. An intracranial pressure (ICP) monitor was placed with initial ICP of 24 mm Hg. Mannitol and 3% saline (0.5–1 mL/kg/hour) were used to maintain cerebral perfusion pressure of 65 to 80 mm Hg. Due to continued ICP elevations (22–64 mm Hg), the patient was placed in a pentobarbital-induced coma with electroencephalographic monitoring (along with vasopressor support).

On hospital day 8, the pentobarbital was discontinued, and the ICP monitor was removed to obtain a second brain MRI. It revealed multiple areas of edema, signal abnormality, and diffusion alteration involving the bilateral putamen, caudate head, thalami, cerebellum, right occipital lobe, and internal capsule consistent with cytotoxic injury (►Fig. 2A–F). In an attempt to minimize, and possibly reverse, persistent MRI-confirmed cerebral edema, pentobarbital and hyperosmolar therapy were continued. After five more days of these ICP-reducing measures, a third MRI showed complete resolution of radiographic manifestations of cytotoxic brain injury (►Fig. 3A–F). In light of the patient's relative stability and the resolutions of cerebral edema on MRI, pentobarbital was discontinued, and within 24 hours, he had spontaneous eye opening with normal brainstem reflexes. He was extubated on hospital day 16 with a steadily improving neurologic examination. Renal function returned, and the patient was discharged on hospital day 38 with a normal neurologic examination.

Discussion

Clinical Progression of Ethylene Glycol Toxicity

Clinical presentation following EG ingestion classically progresses through three stages. The first stage typically occurs

Table 1 Clinical timeline of clinical features and image findings

Date	4 days PTA	2 days PTA	One day PTA	Emergency department	PICU admission	Hospital day 1	Hospital day 8	Hospital day 13
Clinical features	Normal state of health	Headache and emesis	Disorientation, ataxia, diplopia	Worsened disorientation and confusion; positive Romberg's test; finger-to-nose dysmetria; diminished muscle strength; intubated for neurologic deterioration	Comatose but pupils were reactive and equal; tachycardic and hypertensive	Seizures developed; intracranial pressure monitor placed; pentobarbital coma initiated	Intracranial pressure monitor removed	
Image findings			Cranial CT: normal	Brain MRI: normal		Cranial CT: effacement of cerebral sulci and extra-axial cerebral spinal space	Brain MRI: multiple areas of edema, signal abnormality, and diffusion alteration involving the bilateral putamen, caudate head, thalami, cerebellum, and right occipital lobe consistent with cytotoxic injury	Brain MRI: complete resolution of radiographic manifestations of cytotoxic brain injury

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PICU, pediatric intensive care unit; PTA, prior to admission.

less than 12 hours following ingestion and manifests as inebriation similar to ethanol ingestion. As EG metabolism progresses, neurologic symptoms can progress to include altered mental status, ataxia, nystagmus, seizures, hypotonia, coma, and cerebral edema. The second stage usually develops 12 to 24 hours postingestion and involves cardiopulmonary toxicity including tachycardia, hypertension, metabolic acidosis with hyperventilation, and hypoxia secondary to aspiration, congestive heart failure, or adult respiratory distress syndrome. The third stage occurring 24 to 72 hours following ingestion is characterized by oliguria or anuria and renal failure requiring hemodialysis.² Some authors also describe a fourth stage in EG poisoning. Occurring 6 to 13 days following ingestion, this phase consists of central nervous system (CNS) involvement with anisocoria, blurred vision, dysphagia, vomiting, ataxia, areflexia, and cerebral edema.^{11,12} While the time of ingestion was uncertain, our patient likely presented between stages 3 and 4.

The lethal dose of EG is difficult to determine due to the reliance on an estimation of the quantity ingested, the timing of EG level acquisition, and a wide range of fatal EG amounts reported in the literature (20–430 mg/dL).¹³ Our patient had an admission EG level of 179 mg/dL, which may not reflect a true peak as he was symptomatic 2 days prior to admission.

Calcium oxalate crystal formation plays a role in the pathophysiology of EG toxicity. CNS calcium oxalate deposition from EG poisoning has been described since the 1940s, with parenchymal and perivascular deposition throughout the brain (a finding typically noted postmortem).^{3,5,6,8,9,14} Specific clinical manifestations of calcium oxalate deposition are speculative, though it is likely associated with signs and symptoms of increased ICP^{8,12,15–17} and postmortem cerebral edema.^{5,8–10} Chemical meningoencephalitis and aseptic meningitis with neutrophils and lymphocytes in the cerebral spinal fluid have also been linked to calcium oxalate deposition.^{5–8,15}

Neuroimaging in Ethylene Glycol Toxicity

As in our case, neuroimaging is frequently employed in patients with CNS manifestations secondary to EG intoxication. In a review of the current literature, 16 case reports of EG ingestion in which neuroimaging was used for evaluation and management were found; these are described in ► **Table 2**. Including our patient, ages ranged from 17 (ours) to 64 years. An EG level was obtained in 11 cases, with an average value of 190 mg/dL (4–1055.5 mg/dL). As with our patient, 11 patients went on to have a full or nearly full neurologic recovery, and 5 patients died due to complications from the ingestion, including renal failure, gastrointestinal hemorrhage, and coma/brain death. One study used MRI initially,¹⁸ whereas all other studies used CT. All but one patient¹⁴ had at least one subsequent imaging study, with MRI being used much more frequently (11/20 follow-up imaging studies).

Initial imaging was completed within the first 3 days of admission in those studies in which the timing was reported. Initial neuroimaging revealed abnormalities in 12 patients, with the basal ganglia and thalamus being affected the most.

Fig. 2 Magnetic resonance imaging images from hospital day 8, demonstrating edema and signal abnormality of bilateral putamen, caudate head, thalami, internal capsule, and cerebellum. (A) T2-weighted image of the basal ganglia. (B) Fluid attenuated inversion recovery (FLAIR) sense image of the basal ganglia. (C) Diffusion-weighted image (DWI) of the basal ganglia. (D) T2-weighted image of the cerebellum. (E) FLAIR sense image of the cerebellum. (F) DWI of the cerebellum.

Fig. 3 Magnetic resonance imaging images from hospital day 13, demonstrating resolution of abnormalities. (A) T2-weighted image of the basal ganglia. (B) Fluid attenuated inversion recovery (FLAIR) sense image of the basal ganglia. (C) Diffusion-weighted image (DWI) of the basal ganglia. (D) T2-weighted image of the cerebellum. (E) FLAIR sense image of the cerebellum. (F) DWI of the cerebellum.

Table 2 The use of neuroimaging for the evaluation and management of patients with ethylene glycol ingestion

Author, year	Age, EG level	Initial imaging	Subsequent imaging	Patient outcome
Maier, 1983 ²¹	33 y, 110 mg/dL	CT: edema; temporal lobe (HD 2)	CT: edema (HD 6)	Full neurologic recovery
Bobbitt et al, 1986 ¹⁵	36 y, 465 mg/dL	CT: edema (HD 3)	CT: central atrophy (HD 17)	Full neurologic recovery
Chung and Tusso, 1989 ¹²	33 y, 187 mg/dL	CT: normal	CT: edema, leukoencephalopathy (HD 11)	CT: decreased edema (within 1 mo)
Steinke et al, 1989 ¹⁷	30 y, 4 mg/dL (frozen serum)	CT: edema; brain stem, basal ganglia and white matter (HD 2)	CT: external capsule (HD 10)	CT: normal brain (HD 35, 5 mo)
Zeiss et al, 1989 ²²	29 y	CT: edema; basal ganglia (HD 2)	CT: basal ganglia (3 wk)	Death due to persistent renal failure and coma (3 wk)
Lewis et al, 1997 ¹⁶	31 y, 39 mg/dL	CT: normal	MRI: fifth cranial nerve, communicating hydrocephalus (HD 10)	Almost full neurologic recovery
Morgan et al, 2000 ²⁵	26 y, 44 mg/dL	CT: pons, midbrain, thalami and basal ganglia (HD 3)	MRI: basal ganglia (24 days)	Full neurologic recovery
Caparros-Lefebvre et al, 2005 ²⁴	50 y, 110 mg/dL	CT: basal ganglia	CT: basal ganglia (2 wk)	CT: cortical atrophy MRI: basal ganglia (6 mo)
Froberg et al, 2006 ¹⁴	25 y, 55 mg/dL	CT: cerebellum (admission)	CT: edema (8 h)	Death within 24 h
Freilich et al, 2007 ²⁸	43 y, 14.7 mg/dL	CT: vasculature	CT: negative (HD 2), MRI: white matter (HD 8)	MRI: negative (6 mo)
Takahashi et al, 2008 ¹⁹	20s	CT: normal	CT: edema	Brain death
Moore et al, 2015 ²³	20 y	CT: edema; basal ganglia, thalami, white matter	MRI: basal ganglia, thalami, temporal lobe, and brainstem	Full neurologic recovery
Corr and Szólics, 2012 ²⁶	59 y	CT: basal ganglia and external capsule (admission)	MRI: basal ganglia	Death (GI bleed)
Agarwal and Vancil, 2012 ¹⁸	37 y	MRI: basal ganglia and thalami		Full neurologic recovery
Ahmed et al, 2014 ²⁰	64 y, 1,055.5 mg/dL	CT: normal (admission)	MRI: thalami and pons	Full neurologic recovery
Garg et al, 2015 ²⁷	58 y	CT: multiple infarcts	MRI: edema; scattered infarcts	Death (withdrawal)
Owen et al, this study	17 y, 179 mg/dL	CT and MRI: normal (PTA)	CT: edema (HD 1)	MRI: edema; basal ganglia, thalami cerebellum, and right occipital lobe (HD 8) MRI: complete resolution (HD 13)

Abbreviations: CT, cranial computed tomography; EG, ethylene glycol; GI, gastrointestinal; HD, hospital day; MRI, magnetic resonance imaging; PTA, prior to admission.

Note: The table lists both specific areas noted to be abnormal and/or more diffuse involvement (i.e., edema). When known, the patient's initial EG level and timing of neuroimaging study in relation to hospital admission is given.

Cerebral edema was noted in 5 of the 12 patients. Similar to our case, 4 of 16 patients had normal initial neuroimaging, but were noted to have abnormalities on subsequent studies. Two of these patients went on to have full neurologic recovery.

Our review of the literature revealed that cranial CT is frequently used for initial and ongoing neurologic evaluation of EG ingestion. Depending on the timing of the initial test, head CT may be normal (as was the case with our patient) or exhibit cerebral edema.^{12,16,17,19–23} Various descriptions of EG effects on CT of the brain exist throughout the literature. Typical findings include hypodensities or hemorrhage within the basal ganglia, thalami, midbrain, pons, and temporal lobes.^{17,23–25} Zeiss et al describe a patient with diffuse cerebral edema and low attenuation of the central white matter of the cerebellum, pons, mesencephalon, mediobasal temporal lobes, thalamus, and lentiform nuclei 2 days following EG ingestion. Imaging 3 weeks later showed resolution of edema with persistent low-density areas in the thalami and medial globus pallidus. The patient died due to renal failure and coma. Maier describe hypodense areas in the thalamus, basal ganglia, pons, corpora quadrigemina, and basal portions of the temporal lobes (a presentation similar to our patient) that resolved 4 days later.²² The patient went on to have a full neurologic recovery.²¹ As previously described, our patient initially had a normal head CT that progressed from mild to severe cerebral edema on hospital day 1, with resolution of findings (with the exception of residual edema at the site of the ICP monitor) on hospital day 16.

MRI use in this population is becoming more routine. After 1997, all but two patients in our review had at least one MRI during their hospitalization. Initial MRI scans were generally obtained within a few days of ingestion but some as late as 6 months after EG consumption. Similar to CT, abnormalities were typically seen in the basal ganglia, thalami, temporal lobe, and brainstem,^{18,20,24–27} with a few interesting exceptions. Lewis et al reported a patient with cranial nerve dysfunction, bilateral fifth cranial nerve inflammation, dilatation of the lateral ventricle temporal horns, and communicating hydrocephalus on an MRI obtained 11 days after EG ingestion. The patient survived with a near full resolution of her neurologic symptoms and a normal MRI 3 months post-ingestion.¹⁶ Freilich et al reported an MRI with nonspecific cerebellar white matter abnormalities 5 days post-ingestion with subsequent resolution 6 months later.²⁸ Moore et al reported hyperintensities within the basal ganglia, thalami, amygdala, hippocampus, and brainstem, with restricted diffusion within the white matter tracts of the corona radiata likely due to cytotoxic edema. Their patient also went on to make a full recovery.²³ Of note, 8 of 10 patients (including our own) with an abnormal MRI at some point during their hospitalization went on to have a full neurologic recovery, suggesting that much of the neurologic injury visible on MRI is recoverable.

Conclusion

This case demonstrates the evolution and reversibility of CT and MRI brain changes in some EG-poisoned patients. Other

case reports have also shown resolution of brain pathology following EG toxicity. This case reinforces the notion that CNS manifestations from EG poisoning may not show up on initial neuroimaging. Furthermore, our case suggests that unlike other causes of cerebral edema such as traumatic brain injury and hypoxic-ischemic encephalopathy, abnormal neuroimaging in the EG-intoxicated patient may not be as useful for prognostication and extent of injury as most patients in our review with MRI abnormalities went on to have full neurologic recovery.

Note

Our Investigational Review Board deemed our case report exempt from review.

Conflict of Interest

None.

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