Autonomic Dysfunction as a Delayed Sequelae of Acute Ethylene Glycol Ingestion

A Case Report and Review of the Literature

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Abstract Ethylene glycol poisoning is a common form of poisoning worldwide. The clinical course of ethylene glycol poisoning usually follows a three-stage progression, although these stages may overlap. A fourth stage of delayed neurological dysfunction consisting of cranial neuropathies has been suggested in several case reports. We describe a patient with unique findings of postural hypotension and gastroparesis following ethylene glycol toxicity with the additional uncommon features of albuminocytologic dissociation and increased intracranial pressure with papilledema. In addition, we provide a review of the literature on delayed neurological manifestations in ethylene glycol toxicity and further elucidate a description of a fourth stage of delayed neurological dysfunction following ethylene glycol poisoning.

Keywords Ethylene glycol poisoning · Neurological sequelae · Autonomic dysfunction · Postural hypotension · Gastroparesis

Introduction

Ethylene glycol (EG) poisoning is a relatively common occurrence worldwide that can lead to significant morbidity

and mortality [1]. Ethylene glycol ($C_2H_6O_2$) has a small molecular weight enabling it to increase the osmol gap early in toxic ingestions. However, it is EG's metabolism in the liver and the production of its toxic metabolites (glycoaldehyde, glycolic acid, glyoxalate, and oxalate) that are responsible for most of the clinical manifestations of poisoning.

The clinical course of ethylene glycol poisoning usually follows a three-step progression, the stages of which may overlap considerably [2, 3]:

Stage 1 (0.5 to 12 h post ingestion) consists of central nervous system (CNS) symptoms of inebriation, ataxia, seizure, coma and, with large enough doses, death. Irritation to the stomach may cause nausea and vomiting. Stage 2 (12 to 24 h post ingestion) is a result of accumulation of organic acids leading to cardiopulmonary syndrome that manifests as tachycardia, hypertension, tachypnea and pulmonary edema (cardiogenic and noncardiogenic). Stage 3 (24 to 72 h post ingestion) consists of renal failure resulting from osmotic damage and calcium oxalate deposition in the kidney. Metabolic acidosis can be found in all three stages of EG poisoning.

An additional stage four (days to weeks after ingestion) that manifests as delayed neurological deficits was originally suggested by Factor and Lava [4] in 1987 based on three case reports exhibiting cranial nerve deficits [5–7] following EG poisoning. The manifestation of this finding was likely due to better survival outcomes of severe EG poisoning which was often fatal in the first three phases before widespread use of hemodialysis. Since then, there have been other cases reporting findings of delayed cranial neuropathies [8–19]. Reports also describe cerebral edema [20, 21], seizures [20, 22], increased intracranial pressure with

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papilledema [16] and communicating hydrocephalus [11], stroke [14, 23, 24] (one of which involved development of rapid onset Parkinson disease due to basal ganglia hemorrhagic infarction [24]), diaphragmatic paralysis [13], sensory radiculopathies [10, 12, 17, 25], cerebrospinal fluid (CSF) findings of albuminocytologic dissociation [4, 9, 13, 25] as well as aseptic meningitis [8, 21, 26]. Some features of autonomic nervous system (ANS) dysfunction such as the bradycardia/tachycardia syndrome [14] and urinary retention with paralytic ileus [17] were reported; however, to our knowledge, *postural hypotension* and *confirmed gastroparesis* have not been previously described. Vomiting with delayed transit by barium follow through [12] has been reported; however, this is not a confirmatory test for gastroparesis and could represent a paralytic ileus. We report a case of EG poisoning that resulted in ANS dysfunction with postural hypotension and confirmed gastroparesis with the additional uncommon features of albuminocytologic dissociation (as seen in Guillain–Barre syndrome) and increased intracranial pressure with papilledema. We provide a review of late neurological manifestations of EG poisoning and further characterize a fourth stage of this illness consisting of delayed neurological dysfunction.

Case Report

An 18-year-old white male with a history of depression was brought to the emergency department in a state of confusion and agitation. His suicidal note stated that he had ingested half a gallon of ethylene glycol 10 h prior. On presentation he was tachycardic at 109 beats/min, his blood pressure was 178/100 mmHg and his respiratory rate was 22 breaths/min. He appeared combative and confused; the rest of the physical examination including his neurological examination was unremarkable. The patient was intubated for airway control and 100 g of activated charcoal was given via a nasogastric tube. Initial laboratory studies revealed a leukocytosis of 27,000 per cm^3 , blood urea nitrogen (BUN) of 11 mg/dl, serum creatinine concentration of 1.5 mg/dl, glucose of 145 mg/dl, serum sodium (Na) was 141 mmol/l, chloride (Cl) was 104 mmol/l and bicarbonate (HCO_3) of 6 mmol/l (anion gap was 31). An arterial blood gas was significant for evidence of metabolic acidosis with a serum pH of 7.05 and a PCO_2 of 35 mmHg, HCO_3 of 9.5 mmol/l, and a serum lactate of 9.7 mmol/l. His measured serum osmolality was 356 mOsm/kg, his calculated serum osmolality was 294 mOsm/l yielding an osmol gap of 62 mOsm/kg. His serum alanine aminotransferase (ALT) was 72 units/dl, aspartate aminotransferase (AST) was 50 units/dl and a total bilirubin was 0.8 mg/dl. A serum toxicology screen for acetaminophen, salicylate, ethanol, and methanol was negative. A serum EG concentration was

1958 $\mu\text{g/ml}$ (195 mg/dl). An electrocardiogram (EKG) was remarkable for sinus tachycardia of 109 beats/min and his chest radiograph was within normal limits. He was started on a continuous intravenous infusion of bicarbonate, was given appropriate intravenous doses of fomepizole (loading dose of 1.6 g followed by a maintenance dose of 1.1 g every 12 h for an additional two doses), and single doses of folate (100 mg), thiamine (100 mg) and pyridoxine (50 mg). The patient was emergently hemodialyzed for EG poisoning 5 h after initial presentation. Over the ensuing 16 h, the patient became anuric with a rising serum creatinine concentration. His metabolic acidosis progressively improved (pH 7.38, pCO_2 35 mmHg, HCO_3 23 mmol/l) and serum osmolality improved to 284 mOsm/kg. The patient was extubated 39 h after presentation to the ER. Hemodialysis was continued for his renal failure.

On day 13 of his hospitalization, the patient complained of a headache, photophobia, and blurring of vision with diplopia. Ophthalmological and neurological examinations revealed bilateral papilledema with normal visual acuity and a left sixth cranial nerve palsy. A lumbar puncture revealed a raised opening CSF pressure of 31 cm of H_2O (normal <21 cm of H_2O), a glucose of 61 mg/dl, a protein of 157 mg/dl and zero white blood cells (albuminocytologic dissociation). Magnetic resonance imaging (MRI) with gadolinium of the patient's head was within normal limits. The patient was started on acetazolamide to treat his elevated intracranial pressure with papilledema. One week later, the patient developed a left seventh cranial nerve palsy, and evidence of a sensory neuropathy in both feet (sharp pain and paresthesias on plantar surfaces). Strength, deep tendon reflexes, sensation to touch, temperature and vibration were all normal. Gabapentin was initiated to treat the neuropathy with improvement in symptoms noted.

In addition, the patient started to complain of dizziness on standing and was found to have postural hypotension (supine BP, 141/81 mmHg, standing BP, 108/66 mmHg) which did not resolve despite discontinuing his anti-hypertensive medications (labetolol and amlodipine). He also complained of persistent nausea and vomiting after meals. A gastric emptying study done 4 weeks after initiation of gastrointestinal symptoms showed mildly delayed gastric emptying of 111 min (normal, up to 90 min). His symptoms improved on oral metoclopramide of 10 mg every 6 h as needed.

Hemodialysis was discontinued 40 days after the initial presentation due to recovery of renal function and the patient was discharged home. The sixth and seventh cranial nerve palsies, papilledema, sensory radiculopathies and gastroparesis gradually resolved by 3 weeks after discharge; however, he continued to have asymptomatic orthostatic hypotension off all medications.

Table 1 Published case reports of delayed neurological dysfunction after ethylene glycol intoxication

Author (year)	Age (years)/gender	Ingested dose	Treatment	Delayed neurological dysfunction	Onset (days)	Neurological outcome
Berger [5] (1981)	21 M	120 ml of antifreeze	HD, Fomepizole	Dysarthria, dysphagia, b/l facial weakness, decreased visual acuity, anisocoria, dysmetria	6	Recovered after 1 month
Fellman [6] (1982)	22 M	Not reported	PD followed by HD	Ataxia, Lt arm chorea, deviation of tongue	8	Recovered in 7 months, chorea and broad-based gait persisted
Malaya [7] (1986)	26 M	200 ml of antifreeze	Not reported	Dysarthria and dysphagia	13	
Bobbitt [20] (1986)	36 M	Not reported	Ethanol, HD, Dexamethasone	Facial diplegia	15	
Factor [4] (1987)	46 M	Not reported	PD followed by HD	B/l facial nerve palsies, neurosensory hearing loss, dysphagia	11	Facial weakness and dysphagia persisted after 1 year
Palmer [8] (1989)	57 M	Not reported	HD	Cerebral edema, seizure, coma	3	Recovered in 17 days
Palmer [8] (1989)	53 M	Not reported	HD	Facial diplegia, b/l optic nerve dysfunction	14	Recovered in 1 month
Spillane [9] (1991)	33 M	1 quart of antifreeze	Ethanol, HD	Dysarthria, CNs: V, VII, VIII deficits	11	Neurological dysfunction persisted on day 22 (patient expired after cardiac arrest)
Spillane [9] (1991)	22 M	75 ml of EG	HD	Deafness from involvement of cochlear part of CN VIII	8	Neurological dysfunction persisted at 1 year (patient expired after cardiac arrest)
Sydr [10] (1996)	39 M	200 ml of antifreeze	HD	CNs: IX, X deficits B/l CN VII deficit	5 9	CNs deficits persisted at 45 days, patient was lost to further follow up
Lewis [11] (1997)	31 F	Not reported	Ethanol, HD, Thiamine, Folate, Pyridoxine	B/l CN VII defect	14	Facial nerve palsy persisted after 3 months
Broadly [12] (1997)	43 M	250 ml of antifreeze	HD	Rt CN VII palsy, neurosensory deafness, polyradiculopathy, albuminocytologic dissociation in CSF	14	Recovered in 2 months
Auzepey [13] (1997)	35 M	Not reported	HD, Ethanol	CNs: II, V, VII, VIII deficits	10	Complete recovery in 11 months
Morgan [14] (2000)	26 M	1/2 gallon of antifreeze	Ethanol, HD, Charcoal, Thiamine, Pyridoxine	Neurosensory deafness, b/l facial CN palsies, b/l optic atrophy, SM radiculopathies, delayed transit time by barium follow through	7–10	5 months later patient was walking with assistance device with persistent optic atrophy
				Facial CN palsy, paralysis of diaphragm, SM neuropathy	11	Resolution of diaphragmatic paralysis in 1 month, SM neuropathy in 3 months, facial nerve palsy in 10 months
				Bradycardia, bradypnea with hypodensities in basal ganglia, midbrain and pons on CT	3	Recovered over 4 months
				B/l CN VI palsy	7	

Table 1 (continued)

Author (year)	Age (years)/ gender	Ingested dose	Treatment	Delayed neurological dysfunction	Onset (days)	Neurological outcome
Jaffery [22] (2001)	25 M	10 ml of EG	HD	Seizures with Lt frontal and Rt parietal infarction on MRI	7	Seizure free in 8 weeks
Tobe [15] (2002)	23 M	12 units of alcohol (EG)	HD	Deafness, dysphagia, dysarthria, complete flaccid paralysis	7	Able to breathe spontaneously in 2 months, able to walk with crutches after 16 months, complete deafness persisted
Zhou [24] (2002)	40 M	Not reported	Not mentioned	Polyradiculopathy	12	Persisted after 17 days, lost to further follow up
Delancy [16] (2004)	34 M	Not reported	HD	Lt CN VI palsy, papilledema with increased ICP on LP	7	Recovery of CN deficits in 4 weeks
Ohmori [23] (2004)	36 M	200 ml of EG	HD	Miosis, external ophthalmoplegia with low density areas in b/l basal ganglia, mid-brain and pons on CT scan	4	Complete recovery in 36 days
Martinez [17] (2006)	25 M	920 ml of antifreeze	HD	SM polyradiculopathies, CNs: V, VII, IX and X palsies, paralytic ileus, urinary retention	8	Recovery in 37 days
Reddy [24] (2007)	36 F	Not reported	IV Ethanol, HD	Acute onset Parkinson disease from hemorrhagic infarction of basal ganglia (GP, putamen) on MRI	9	Improvement in Parkinson disease within 24 h of starting Levodopa, at 17 days less bradykinetic
Ting [18] (2009)	49 M	Not reported	HD, Ethanol	Rt CN VII palsy	4	Full recovery in 3 months
Baldwin [19] (2010)	53 M	Not reported	CVVH	B/l palsies of CNs III, VI and VII, SM radiculoneuropathy, albuminocytological dissociation	14	Recovery in 10 weeks but neuropathic pain persisted
Our case	18 M	1/2 gallon of antifreeze	HD, Fomepizole, Charcoal, Thiamine, Folate, Pyridoxine	Lt CN VI palsy, b/l papilledema, albuminocytological dissociation Lt CN VII palsy, sensory radiculopathies, gastroparesis, postural hypotension	13 20	Complete recovery of CN palsies, papilledema, sensory radiculopathies, and gastroparesis but persistence of postural hypotension at 9 weeks, lost to further follow up

M male, *F* female, *EG* ethylene glycol, *HD* hemodialysis, *PD* peritoneal dialysis, *CN* cranial nerve, *Rt* right, *Lt* left, *b/l* bilateral, *IV* intravenous, *CT* computed tomography, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *LP* lumbar puncture, *GP* globus pallidus

Discussion

Our patient had evidence of ANS dysfunction in the form of radiologically confirmed gastroparesis and postural hypotension; this has not been previously reported as a complication of EG poisoning. None of his medications are known to cause postural hypotension. He received supplemental thiamine and pyridoxine to replenish the respective cofactors during his early hospitalization; thus ruling out their deficiencies as a cause of his neuropathy. Our patient also had the additional uncommon features of albuminocytologic dissociation and increased intracranial pressure with papilledema. This has been described previously in only a few cases as delayed neurotoxicity following EG intoxication.

The originally reported delayed cranial nerves abnormal signs and symptoms occurring five to 20 days later [11] are unlikely to be explained by the immediate formation of toxic metabolites. Similarly, since tissue deposition (particularly in the kidneys, brain and lungs) of calcium oxalate crystals occurs within 3 to 6 h of ethylene glycol ingestion [11], the direct deposition of calcium oxalate crystals in the tissues is also an unlikely explanation. Oxalate is a strong reducing agent and is toxic to endothelial cells [21]. Deposition of calcium oxalate crystals in cases of EG poisoning has been documented within small cerebral blood vessels walls and leptomeninges at post-mortem examinations [21, 26]. In 1979, Levinsky et al. [26] demonstrated deposition of calcium oxalate crystals in the walls of cerebral vessels with an infiltrate of neutrophils and mononuclear cells as well as proteinaceous fluid in the meninges and around parenchymal vessels. These changes can result in patchy focal necrosis with or without hemorrhage throughout the brain and chemical meningitis [26]. More recently, Froberg et al. [21] also found calcium oxalate crystals within vessel walls with prominent perivascular edema and collection of polymorphonuclear leukocytes adjacent to these vessels. Histologic evaluation of tissue sections of meninges showed a neutrophilic infiltrate [21]. Both autopsy investigations following EG poisoning have shown edema, hemorrhage and perivascular inflammation adjacent to small blood vessels in the brain suggesting exudative damage to the endothelial cells in these vessels causing nerve dysfunction [21, 26]. The time required to develop an inflammatory response to the endothelial injury may explain the *delay* in neurological sign and symptom manifestations [11, 21] (Table 1 [4–24]).

The ANS dysfunction, sensory radiculopathy and CSF finding of albuminocytologic dissociation observed in our patient likely resulted from vascular involvement and injury to the corresponding brain structures. His ANS dysfunction signs and symptoms may have resulted from involvement of the hypothalamus or vasomotor center [14]. The sensory radiculopathy and CSF findings may have resulted from meningeal involvement covering the nerve roots.

The clinical outcome of patients reported to have developed these delayed neurological findings is variable (Table 1) [4–24]. An overwhelming majority of patients who developed the fourth phase of EG toxicity were males (22 cases out of total 24). In those patients in whom treatment was reported, all underwent dialysis. The initial onset of delayed neurological symptoms varied from 3 to 20 days (confirming observation made by Lewis et al. [11]) with an average of 9 days after ingestion of EG. A significant number of patients recovered their neurological function in 1 to 2 months after onset; in some patients the neurological deficits took longer to resolve and yet in others the neurological dysfunction persisted at 1 year of follow-up. The fastest recovery of neurological manifestations (17 days) was observed in a case treated with Dexamethasone [20].

We hypothesize that the fourth phase of delayed neurological dysfunction is not limited to cranial nerve deficits but encompasses all features of neurological dysfunction and stems from the inflammatory response due to endothelial injury from calcium oxalate deposition.

In conclusion, physicians treating patients with EG poisoning should be aware of the potential for delayed neurotoxicity. Autonomic nervous system dysfunction manifesting as postural hypotension and gastroparesis can be associated with EG poisoning and should be recognized as part of the delayed neurological complications that can manifest after recovery from acute poisoning. More research is indicated to further elucidate the etiology of the neurological component of this illness.

Conflict of Interests None for all authors.

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