Heliyon 5 (2019) e03005

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

# Opioid-induced toxic leukoencephalopathy: A case report and review of the literature

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ARTICLE INFO

*Keywords:*
Medicine
Neurology
Neuroscience
Pediatrics
Nervous system
Neurosurgery
Critical care
Clinical toxicology
Pediatrics
Opioid ingestion
Toxic leukoencephlaopathy
Pediatrics

ABSTRACT

*Importance:* Reports of toxic leukoencephalopathy (TLE) due to opioids have been extensively documented within the adult literature. There is a paucity of literature with respect to the incidence, complications, and outcomes of TLE in the pediatric population.

*Objective:* To describe a rare complication of opioid ingestion in the pediatric population and serve as the first large review of published cases of opioid-induced leukoencephalopathy. Thirteen case reports with varying treatments are herein reviewed in addition to our own case. The range of treatment modalities, morbidity and mortality are broad and outcomes secondary to supportive care versus neurosurgical intervention is explored.

*Evidence review:* All cases of pediatric opioid-induced toxic leukoencephalopathy published on pubmed and google scholar were included in this review.

*Findings:* We report the case of a 4-year old male surgically treated for acute oxycodone-induced TLE who initially presented with Glascow Coma Scale of 4 and a comatose state for weeks. Over the next several months he recovered with spasticity of all extremities, oral aversion, substantial vision loss, and the ability to speak in short sentences. In addition, we found thirteen other reported cases of opioid-induced leukoencephalopathy reported in the literature. The treatment approaches described range from supportive care alone, to invasive neurosurgical interventions including placement of extraventricular drains, removal of hemorrhagic tissue, and craniectomy. The outcomes of patients with opioid-induced leukoencephalopathy is also variable. Reports demonstrate a range of outcomes that include patients who died to those with no residual neurologic deficits.

*Conclusions:* This review of reported pediatric cases of opioid-induced leukoencephalopathy highlights the importance of early neurosurgical intervention for prevention of devastating outcomes.

## 1. Introduction

Toxic leukoencephalopathy (TLE) describes a spectrum of clinical and histopathological features associated with structural changes to cerebral white matter injured by a leukotoxic agent. Such substances include antineoplastic drugs, immunosuppressive drugs, antimicrobial agents, environmental toxins, and drugs of abuse [1, 2]. Although the exact mechanism of toxicity remains speculative, patterns of injury have been described. Histopathology demonstrates white matter vacuolization and spongiform defects as hallmarks of TLE [1, 2, 3].

## 2. Clinical presentation

Neurobehavioral presentations typically include altered mental status, psychomotor changes, depression, anxiety, visuospatial deficit, coma, or death, while language capabilities are characteristically spared [1, 2, 3]. It is important to note that cases of acute TLE may present with sudden increased intracranial pressure, acute hydrocephalus, and herniation due to predominant cerebellar involvement. Therefore, urgent neurosurgical intervention is necessary. The extensive differential diagnosis of cerebellar injury may lead physicians to investigate and treat

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https://doi.org/10.1016/j.heliyon.2019.e03005
Received 30 May 2019; Received in revised form 30 September 2019; Accepted 5 December 2019

**Table 1.** Summary of published case reports of opioid-induced toxic leukoencephalopathy.

| Author (Year) | Age years (Sex) | Agent | Presentation | Radiographic findings | Management | Outcome | Follow-up |
|---|---|---|---|---|---|---|---|
| Nanan et al (2000) [12] | 14 y (F) | Morphine | Unresponsive, irregular respirations, GCS 3, miosis, bilateral babinksi | Symmetrical T2 enhancement of cerebellar white matter<br>T2 symmetrical high signal from frontal and parieto-occipital white matter | Intubation and mechanical ventilation, supportive care | Somnolent, slow movements, poor facial expression, increased muscle tone | 1 year |
| Anselmo et al (2005) [6] | 3 (M) | Methadone | Comatose, unresponsive, metabolic acidosis | Extensive bilateral hypodensity of cerebellar hemispheres and pons, displacement of cerebellar amygdala, acute hydrocephalus | Dopamine, Mannitol, dexamethasone<br>High dose methylprednisolone | Prompt resolution of ataxia, no residual neurological deficits | 4 Weeks |
| Mills et al (2007)[8] | 3 (F) | Methadone | Unresponsive and labored breathing, GCS 3, hypothermia, hypotension, metabolic acidosis, miosis | Low-density grey and white matter changes with diffuse swelling and impingement of the 4$^{th}$ ventricle | Inotropes, Dexamethasone<br>Extraventricular drain, converted to ventriculo peritoneal shunt | Persistent atrophy of cerebrum and cerebellum, mild spastic diplegia, mild dystonia, assisted ambulation, normal cognitive and language function with mild cortical visual impairment | 4 Months |
| Riascos et al (2008) [9] | 22 mo (M) | Methadone | Unconscious | Abnormal white matter signal intensity without restricted diffusion in bilateral cerebral hemispheres and cerebellum with development of hydrocephalus | Intubation, inotropic support | Brain death | Several weeks |
| Bellot et al (2011) [14] | 2 (M) | Buprenorphrine | Unconscious, GCS 5, fever, chest xray opacities | Non-enhancing bilateral and symmetric hypointense signals on T1 weighted images and hyperintense signals on T2 weighted images of the cerebrum and cerebellum | Intubation, supportive care | No residual neurologic impairment | 4 days |
| Krinsky & Reichard (2012) [2] | 18 (M) | Heroin | Ataxia, dysarthria, nausea, emesis, somnolence, tachycardia | Extensive T2 hyperintensity of splenium, corpus callosum, and internal capsule. White matter edema, small ventricles, sulcal effacement | Not described | Death | 2 Months |
| Reisner et al (2015) [3] | 2 (F) | Morphine and hydromorphone | Lethargy and seizures<br>GCS 4 | Diffuse symmetric T2 hyperintensity and restricted diffusion of white matter. Inconsistent hypointensity of cerebellar hemispheres. Cerebellar edema, causing narrowing of 4$^{th}$ ventricle, mass effect on brainstem, and mild acute hydrocephalus | External ventricular drain transitioned to a ventriculoperitoneal shunt<br>Suboccipital craniectomy<br>C1 laminectomy<br>Decompression and removal of herniated cerebellar tissue and surrounding tonsils | Persistent gross motor delay<br>Nonambulatory<br>Profound visual impairment with eventual recovery of tracking and discrimination | 18 Months |
| Metkees et al (2015) [10] | 15 y (F) | Methadone | Unconscious GCS3 miosis | Diffuse nonenhancingT2 hyperintensities and restricted diffusion in the white matter of both hemispheres | Intubation, inotropic support, supportive care | Death | NA |
| Rando et al (2016) [15] | 14 (M) | Methadone | Unresponsive | Low attenuation in the cerebellum with no evidence of increased ICP | Supportive Care | Ataxia and weakness that was improving slightly at the time of discharge | NA |
| Hosseini et al (2016) [11] | 2y (F) | Opium | Unresponsive | Bilateral cerebellar white matter involvement | High does methylprednisolone | No residual neurologic impairment | 2 months |
| Duran et al (2017) [13] | 10m (F) | Oxycodone | Unresponsive, slow labored breathing leading to respiratory failure | Severe, bilateral cerebellar hypoattenuation with ventral displacement of the cerebellar | External ventricular drain, suboccipital craniectomy, C1 | Mild spasticity and internal rotation of her left leg with gait | 23 months |

(*continued on next page*)

**Table 1** (*continued*)

| Author (Year) | Age years (Sex) | Agent | Presentation | Radiographic findings | Management | Outcome | Follow-up |
|---|---|---|---|---|---|---|---|
| | | | | vermis and compression of the fourth ventricles. | laminectomy. Partial resection of cerebellum | and occasional dystonic posturing of the left upper extremity. | |
| Duran et al (2017) [13] | 25 m (M) | Extended Release Morphine | Erratic breathing progressing to apnea and respiratory arrest | Acute hydrocephalus and extensive, symmetric bilateral cerebellar hemispheric hypoattenuation | External ventricular drain, suboccipital craniectomy, and C1 laminectomy with partial resection of cerebellum | Wide based gait and mild left lower extremity spasticity | 3 months |
| Shrot et al (2017) [5] | 16 | Heroin | Altered mental status, rhabdomyolysis | Diffuse symmetrical infratentorial and supratentorial white matter T2 hyperintensities on MRI | Unknown | Persistent vegetative state | N/A |
| Wheaton et al (2019) | 4 (M) | Oxycodone | Comatose, multi-organ failure GCS 4 | Cerebellar edema with diffuse white matter hypodensity sparing infratentorial regions. Diffuse T2 hyperintensity of cerebral white matter, ventriculomegaly, brainstem compression | Aggressive pharmacological management with induced coma Suboccipital craniectomy, c1 laminectomy, EVD | Spasticity of all extremities, aphasia, ataxia, oral aversion, visual impairment | 4 months |

common causes of cerebellar edema including infectious and post-infectious etiologies leading to costly delays in intervention [4].

## 3. Diagnosis

The triad of toxin exposure, neurobehavioral symptoms, and classic radiographic findings should raise suspicion for opioid-induced leukoencephalopathy [1]. Given that exposure to opioids may not have been witnessed or admitted to, the diagnosis of opioid-induced leukoencephalopathy requires a high degree of clinical suspicion. Characteristic imaging studies have described diffuse symmetric T2-weighted hyperintensity of the cerebral white matter on MRI and diffuse hypodensity of the white matter on CT [2, 5]. Involvement of the cerebellum with fulminant edema is frequently described in cases of TLE, and is thought to be linked to relatively high concentrations of mu opioid receptors in this region. This pattern has been associated with poor outcomes in several instances [2, 5].

## 4. Management

Goals of medical management are to treat increased intracranial pressure and minimize secondary neurologic insults. Hyperosmolar therapies [6, 7], corticosteroids [3, 6, 8] and vasoactive infusions [6, 8, 9, 10] to maintain cerebral perfusion pressure have all been reported. Naloxone is also frequently administered [6, 7, 10, 11, 12, 13]. Surgical procedures are targeted at attenuating increased intracranial pressure [3]. This can be achieved through a host of operative techniques, including placement of an extraventricular drain, ventriculostomy, suboccipital decompressive craniectomy, c1 laminectomy, and evacuation of edematous or hemorrhagic tissue [3, 6, 7, 8]. While precedent exists in the literature for each of these surgical maneuvers, selection of the most appropriate course of action remains at the discretion of the surgeon.

## 5. Prognosis and outcomes

The small number of published case reports (summarized in Table 1) highlight the necessity of early neurosurgical consultation and the potential devastating neurologic outcomes that can occur with toxic leukoencephalopathy secondary to opioid intoxication [2, 3, 4, 6, 8, 9, 10, 11, 14, 15]. Together, these cases demonstrate the breadth of clinical presentation and variation in treatment of patients presenting with severely depressed GCS and leukoencephalopathy. Anselmo et al [6], Hosseini et al [11], Bellot et al [14], and Rando et al [15] describe patients who had placement of an EVD or received only supportive care and suffered minor or no neurologic sequelae. There are also patients in the literature who received only supportive care, such as the patient described by Nanan et al [12] who had similar neurologic outcomes to our patient with significant impairment. That is in contrast to Reisner et al [3], Mills et al [8], and Duran et al, [13] who also illustrated similar neurologic outcomes after undergoing more invasive neurosurgical interventions with decompressive craniotomy, and in once case cerebellectomy. Devastating neurologic outcomes or death, as described by Krinsky and Reischard et al [2], Shrot et al [5], Riascos et al [9], and Metkees et al [10], and are also described, and hoped to be mitigated by early neuro-surgical interventions as were undertaken with our patient. Variation in management and outcomes may be explained by quantity of ingestion and duration of time prior to seeking medical care.

## 6. Historical context

Awareness of opioid-induced TLE with possible acute herniation due to cerebellar involvement in the pediatric population is crucial in context of the ongoing US opioid crisis, which has increased the exposure of children and adolescents to high rates of opioid-related morbidity and

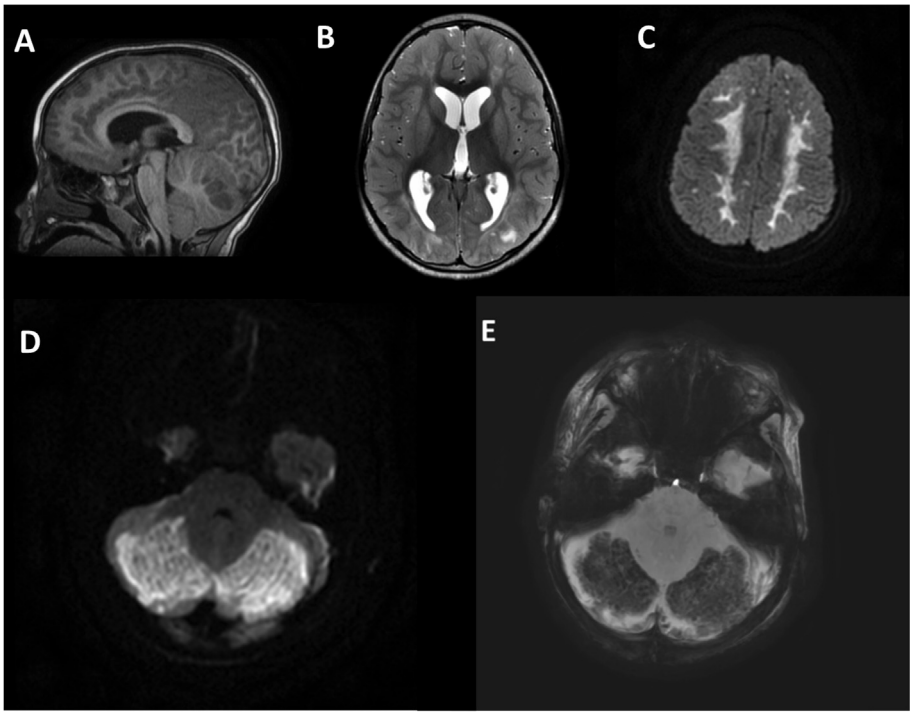


**Figure 1.** Pre-operative MRI. A) Sagittal T1-weighted image showing brainstem compression, B) Axial T2-weighted image showing hydrocephalus, C) Axial DWI showing supratentorial white matter changes, D) Axial DWI showing infratentorial white matter changes, E) Axial gradient echo image showing hemorrhagic conversion.

mortality. Infants and young children are often inadvertently endangered by drugs of abuse related to access by a caretaker or another close individual. The prevalence of drug-induced toxicity is caused by acute exposure [3]. Between 1997 and 2012, the rate of opioid poisoning per 100,000 children in the United States has increased by 165%, and when requiring admission, 43% have required intensive care [16, 17]. Additionally, it has been documented that approximately 20% of American high school students have experimented with illicit substances other than marijuana at least once [5].

We present the case of a 4-year old male treated for opioid induced TLE associated with acute cerebellar edema resulting in increased intracranial pressure and brainstem compression, as well as multi-organ failure. We also review the pediatric literature with respect to this topic. To our knowledge, acute multi-organ dysfunction has not been described in the pediatric presentation of TLE.

## 7. Case presentation

A 4-year old previously healthy male was found unresponsive at home and brought to the emergency room. He was reportedly more tired than usual the day prior to presentation but was otherwise acting normally prior to going to sleep that evening. A review of systems was negative. His examination revealed 2mm bilateral pinpoint pupils with intact corneal reflexes, absent gag reflex, no response to painful stimuli, and extensor posturing (GCS 4). These findings were accompanied by tachycardia (128 bpm), tachypnea (26 breaths per minute), hypoglycemia (49 mg/dL), and hypertension (143/69 mmHg). He had erythematous lesions of various sizes bilaterally over his medial legs, and thorax that later evolved to appear consistent with decubitus ulcers. The patient was emergently intubated for low GCS and inability to protect his airway. Blood gas analysis was not performed prior to intubation but was saturating 100% in room air on arrival.

Initial CT demonstrated cerebellar edema with diffuse white matter hypodensity. A non-contrast MRI (Sagittal T1, T2, coronal T1, T2, Axial T1, T2, Flair, susceptibility weighted and diffusion weighted images) 9 h after initial presentation to the emergency room showed diffuse T2 hyperintensity of cerebral and cerebellar white matter regions, ventriculomegaly, and brainstem compression secondary to 7mm tonsillar herniation through the foramen magnum (Figure 1a-e).

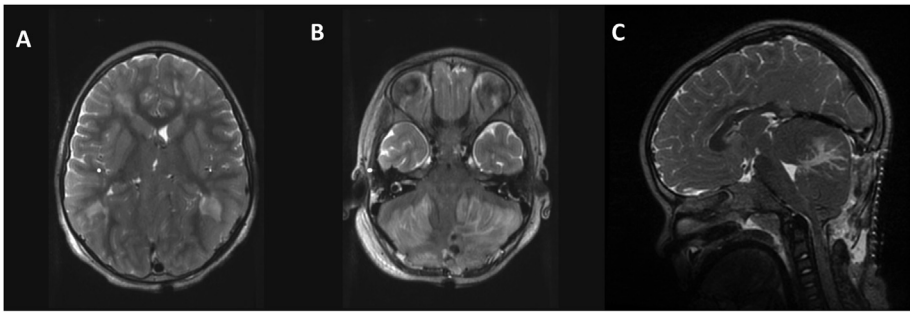


**Figure 2.** Post-operative MRI 2 days after presentation at the time of persistently high ICP. A) Axial T2-weighted image showing decompression of the ventricular CSF, B) Axial T2-weighted image and C) Sagittal T2-weighted image showing persistent compression of the brainstem.

Evidence of hemorrhagic conversion within the cerebellum was present. Laboratory results were consistent with liver and kidney dysfunction, as well as disseminated intravascular coagulation, and rhabdomyolysis. He presented with an arterial serum pH 7.0 with a lactic acidosis of 5.7 mmol/L. A serum oxycodone level of >100 ng/mL was reported in the extended serum toxicology screen, and confirmed by mass spectroscopy (oxycodone = 1360 ng/mL oxymorphone = 6940 ng/mL). Cytochrome P450 2D6 genotyping demonstrated normal metabolic activity. An extended infectious disease workup was negative. Based on his clinical presentation, imaging studies, and laboratory results, he was diagnosed with opioid-induced toxic leukoencephalopathy.

Initial treatment included supportive measures and hyperosmolar therapy for increased intracranial pressure, broad spectrum antibiotics, and high-dose steroids. Naloxone was not administered. Patient received volume boluses and modulation of vasoactives and inotropes to maintain hemodynamics in an effort to optimize cerebral perfusion.

Upon completion of the MRI that displayed herniation, emergent surgical decompression was recommended. The patient was administered activated factor VII and FFP to reverse coagulopathy and was taken to the operating room for placement of an extraventricular drain (EVD), followed by a wide suboccipital decompression with C1 laminectomy, and duraplasty. Given pre-existing coagulopathy and hemorrhagic conversion within the cerebellum pre-operatively, a decision to not excise cerebellar tissue was made intraoperatively. Postoperative imaging two days later (Non-contrast MRI with same sequence parameters) suggested improvement of cerebellar edema and herniation with pervasive sustained signal abnormalities throughout the supratentorial white matter and cerebellum (Figure 2a-c).

He received standard therapy for elevated intracranial pressures (Head-of-bed 30°, hypertonic saline with serum sodium in the 150s, serum osmolality near 320, PCO2 35–40). Subsequently, a medical coma was induced pharmacologically with pentobarbitol due to persistent elevated intracranial pressures (ICP >20 mm$H_20$). His course was further complicated by persistent hypertension and bradycardia, initially thought to be secondary to Cushing reflex, but later attributed to dysautonomia. This improved with the addition of clonidine and diazepam.

Over the course of two weeks, the patient stabilized with a mildly improving neurological examination. Limited recovery of brainstem function was achieved; however, the patient remained neurologically devastated. The pupils increased to 3mm and were reactive with intact corneal reflexes but he did not demonstrate a gag reflex or spontaneous respiratory drive. He remained with extensor posturing bilaterally. The EVD was removed in the PICU at 28 days post-operative with ICPs in the range of the low teens. A delayed MRI (Non-contrast MRI with same sequence parameters) was acquired a month after initial presentation due to persistence of poor neurologic examination, demonstrating less brainstem compression and ventriculomegaly without elevated intracranial pressure with resolution of sulcal effacement (Figure 3a-b) consistent with resolving injury. At this time, care was transitioned to an outside facility.

Four months later, he had surprising improvement of neurologic function. He had significant spasticity of all extremities and moved all with significant impairment. He had oral aversion and required a gastrostomy tube for nutrition but was able to speak in short sentences. He also suffered substantial vision loss. No follow-up MRI was available to report. To date it is unknown whether the ingestion occurred accidently or if his intoxication was due to abuse.

## 8. Discussion

Poor outcomes of this nature are not uncommon in comparable documented cases of TLE with acute cerebellar edema. Associated

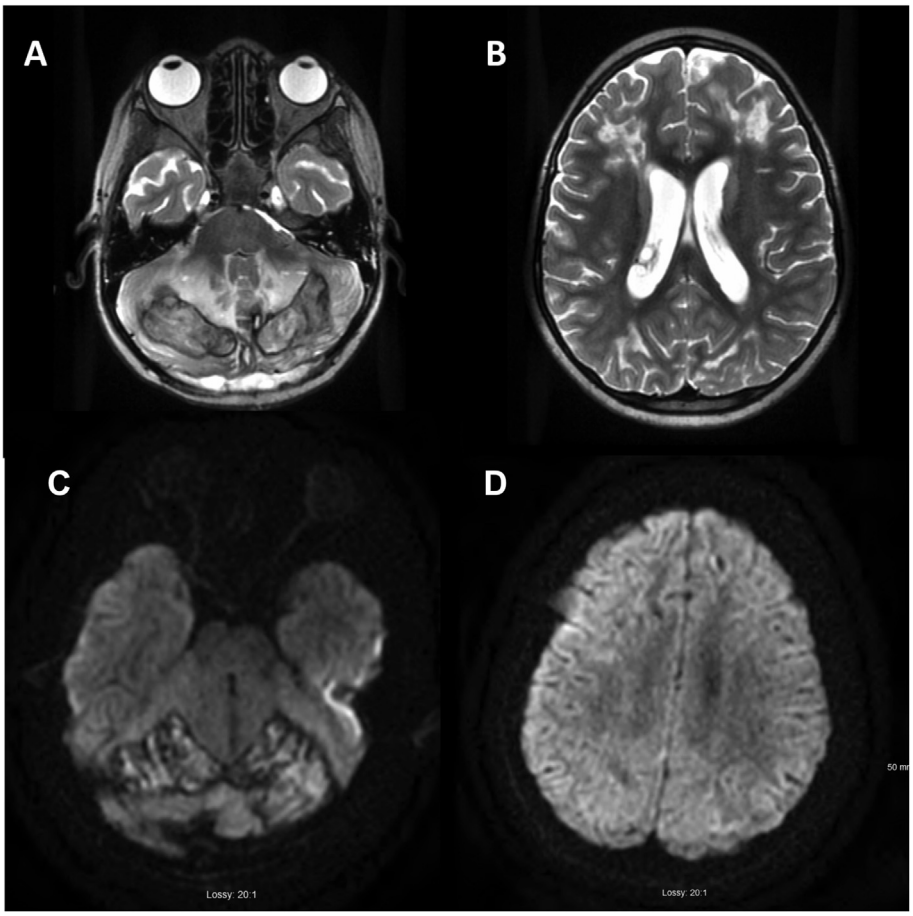


**Figure 3.** Delayed MRI 28 days after presentation after poor neurological examination persisted (A,B) and 20 days after presentation (C, D). A) Axial T2-weighted image showing less brainstem compression, B) Axial T2 image showing ventriculomegaly without elevated ICPs with resolution of sulcal effacement C) Axial DWI showing interval improvement of swelling of the cerebellum with significant decrease in degree of effacement of ventricles D) Axial DWI showing interval improvement of signal abnormality within the cerebellum and cerebrum.

multi-organ failure has not been reported in pediatric literature to our knowledge [2, 5]. We hypothesize that his profound organ dysfunction had a multifactorial etiology. Despite never suffering a full respiratory or cardiac arrest, the patient had a significant period of immobility given that he presented with decubitus ulcers. He did not present hypotensive nor was he desaturated upon arrival. However, he did have an abnormal respiratory pattern which would support a mild hypoxic state leading to delayed post-hypoxic leukoencephalopathy. After a mild episode of hypoxia, neurologic injury of this nature may be reversible, but delayed pathologic demyelination may occur [18]. Imaging was not suggestive of diffuse hypoxic injury, making hypotensive or hypoxic injury unlikely to have caused multi-organ failure. These findings were likely incited by direct cytotoxic effects from oxycodone. Cytotoxic effects of opioids have been well described in the literature, including kidney failure secondary to rhabdomyolysis [19], direct hepatotoxicity [20], and overall an increase in superoxide production leading to formation of reactive oxygen species and thus direct cellular injury [21]. We postulate that vision loss occurred secondary to substantial white-matter injury in the occipital lobes bilaterally. There was no afferent pupillary defect and no retinal ischemia noted on ophthalmologic examination to suggest retinal pathology as a cause of his vision loss. There is a paucity of literature describing varying degrees of multi-organ involvement and neurologic sequelae secondary to opiate ingestion. Although children who presented with low GCS with toxic leukoencephalopathy who recovered with mild or no neurologic deficits have been described [6, 11, 12, 13, 14, 15], we believe that these patients likely presented earlier after ingestion. Earlier access to supportive care in these cases likely lessened the effects of more sustained hypoxic injury that led to worse neurologic injury and multi-organ injury in our patient.

## 9. Conclusions

Our case supports the available pediatric literature detailing poor outcomes in patients with TLE whose imaging studies demonstrate acute hemorrhagic cerebellar edema. In reviewing the published case reports, neurodevelopmental outcomes are quite varied. Our patient's delayed outcome was much better than predicted from the initial and immediate post-op clinical presentation further supporting the possible benefit of aggressive early intervention.

In summary, children with exposure to opioids are at risk for developing TLE. In the pediatric population, practitioners must be aware that TLE may present with sudden increased intracranial pressure and herniation due to cerebellar involvement requiring urgent neurosurgical intervention that is lifesaving.

## Declarations

### *Author contribution statement*

All authors listed have significantly contributed to the development and the writing of this article.

### *Funding statement*

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### *Competing interest statement*

Steven Hwang: is a member of the Zimmer Biomet (speakers bureau)-General disclosure, no conflict of interest.

### *Additional information*

No additional information is available for this paper.

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