Opioid overdose in a child: case report and discussion with emphasis on neurosurgical implications

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In environments in which opioids are increasingly abused for recreation, children are becoming more at risk for both accidental and nonaccidental intoxication. In toxic doses, opioids can cause potentially lethal acute leukoencephalopathy, which has a predilection for the cerebellum in young children. The authors present the case of a 2-year-old girl who suffered an accidental opioid overdose, presenting with altered mental status requiring cardiorespiratory support. She required emergency posterior fossa decompression, partial cerebellectomy, and CSF drainage due to cerebellar edema compressing the fourth ventricle. To the authors’ knowledge, this is the first report of surgical decompression used to treat cerebellar edema associated with opioid overdose in a child.

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Opiates are drugs derived from opium, and opioids are synthetic narcotics that have opiate-like actions.4 Opioid overdose in children is usually related to access to pain medication or illicit drugs used by someone else in the household.2,3,4 Most of the morbidity and mortality attributable to opioid use occurs after acute ingestion.2,3,4 In particular, hypoxia, anaphylaxis, pulmonary edema, acute respiratory acidosis, and aspiration pneumonitis are life-threatening complications of opioid overdose demanding urgent attention.2,3,4,11 The use of naloxone and physiological support are often sufficient to result in full recovery.2,3,5,6,11,20,34 However, both immediate and delayed effects of opioid overdose can potentially result in severe neurological complications related to hypoxia and the direct toxic insult introduced by the drug.9,10

Prompt diagnosis and treatment are mandatory for successful outcomes in these patients. Often, as in this case, the radiological features are highly suggestive, if not pathognomonic, of the diagnosis prior to toxicological confirmation.2,21,31,37 In cases in which there is opioid-induced acute cerebellitis, neurosurgical intervention may be required in the form of a ventriculostomy and/or suboccipital decompressive craniectomy for acute hydrocephalus and cerebellar edema with herniation, respectively. This report specifically highlights the neurosurgeon’s role in diagnosing and treating children with opiate-induced acute cerebellitis.

Case Report
Initial Presentation and Management

A 2-year-old girl with no significant medical history presented to the emergency department with lethargy and possible seizure activity. At presentation, her initial neurological examination was consistent with a Glasgow Coma Scale score of 4. She was resuscitated and intubated for airway protection. An emergency noncontrast CT scan of the head revealed symmetric low attenuation in the white matter of the cerebrum and cerebellar hemispheres and effacement of the prepontine cistern (Fig. 1). There was
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minimal effacement of the basilar cisterns and fourth ventricle without significant hydrocephalus. Naloxone was administered without effect. A urine toxicology screen was positive for opiates.

Hospital Course

The patient was admitted to the pediatric intensive care unit (PICU) for serial neurological examinations and supportive care. Noncontrast MRI of the brain obtained 6 hours after the CT scan of the head demonstrated diffuse, symmetric T2 hyperintensity and restricted diffusion in the white matter, consistent with opioid-induced leukencephalopathy (Fig. 2). Some atypical T2 hyperintensity and restricted diffusion were present in the right caudate nucleus and hippocampus, possibly related to seizure activity (Fig. 5). A patchy hypointense signal was demonstrated in the cerebellar hemispheres on the susceptibility-weighted imaging sequence, possibly related to petechial hemorrhages (Fig. 4). The MR image revealed significant progression of cerebellar edema, narrowing of the fourth ventricle, mass effect on the brainstem, and mild acute hydrocephalus, all new since the initial CT scan of the head (Fig. 5). Soon after readmission to the PICU after MRI, the patient became unstable with hemodynamic changes and posturing. Blood toxicology studies revealed significantly elevated levels of morphine and mildly elevated levels of hydromorphone in the serum, consistent with presumed ingestion of a sustained-release morphine formulation such as morphine sulfate. A decision was made to intervene surgically, given both the clinical and radiological progression, despite medical treatment.

Operative Course

The patient was taken to the operating room for emergency surgery. An external ventricular drain was first placed via the right frontal approach. A suboccipital craniectomy and C-1 laminectomy were performed. The dura remained tense and nonpulsatile, despite CSF drainage. Thus, a durotomy was performed. Herniated swollen, hemorrhagic cerebellar tissue was removed. The remaining intradural contused cerebellum remained nonpulsatile, and after observing for a few minutes, continued to swell. Given the concern for imminent brainstem compression, the cervicomедullary region was decompressed by removing the cerebellar tonsils. To ensure adequate decompression, and to safeguard against potential further infracted cerebellar swelling, the lateral third of each cerebellar hemisphere was removed. The lateral medullary cisterns were visualized and the remaining cerebellum became pulsatile. A dural patch graft was placed to minimize the risk of postoperative CSF leak.

Postoperative Course

The patient was unable to successfully wean from an external ventricular drain and therefore required ventriculoperitoneal shunt placement. Initially, she demonstrated significant neurological sequelae including cognitive and motor deficits. She underwent several months of aggressive inpatient rehabilitation, and at discharge had minimal speech, limited purposeful movement, and no serviceable vision. She continued to participate in outpatient physical, occupational, and speech therapy.

At 18 months after her surgery, she demonstrated persistent gross motor delay and remained nonambulatory,

FIG. 1. Initial noncontrast CT scan of the head (left) demonstrates symmetric low attenuation in the cerebellar hemispheres (arrows) with mild effacement of the cisterns without hydrocephalus. Low attenuation in the white matter of the cerebral hemispheres (arrows) is subtle (right).

FIG. 2. Follow-up MRI of the girl’s brain demonstrated symmetric T2 hyperintensity in the cerebellar hemispheres (A) with associated hypointensity on the apparent diffusion coefficient map (B) and hyperintensity on the isotropic sequence (C), indicating restricted diffusion.
but was crawling and cruising. Her speech had improved, and she was able to form short sentences. She had begun to demonstrate light perception in both eyes with tracking and light/dark discrimination.

**Discussion**

**Clinical Presentations**

Opioid abuse no longer occurs primarily via the traditional routes of intravenous heroin injection or smoking of the heroin vapor. Currently abuse is predominantly related to the use of prescription morphine-containing medications. This abuse has reached epidemic proportions in the US. As such, both accidental and intentional ingestion by children is increasingly frequent. In adolescents, opioids are now more commonly abused than marijuana. Kintz et al. reported that the increased number of cases of methadone poisoning in infants paralleled the increase in patients treated with methadone on an outpatient basis. In a nearly 4-year-long study in the English town of Merseyside, 42 children were reported with methadone intoxication. Methodone overdose in children in the US is significant as well. In our case, the overdose was reportedly related to the child finding and ingesting the addicted mother’s prescription drugs hidden between the seats in the car.

Fortunately, significant opioid exposure remains something rare in children. However, when it does occur, the neurological effects and sequelae can result in significant long-term morbidity. A multitude of toxic effects of opioids have been reported, including systemic and CNS effects. The most common symptoms were varying degrees of CNS depression, suppression of the respiratory center with resultant hypercapnia, and respiratory acidosis with miosis. Methadone intoxication in children can present similar to other narcotic intoxications, with dose-dependent depression of the CNS. In a review of 63 cases of pediatric methadone poisoning, Glatstein et al. found that 72% of the children were symptomatic. For those patients who present in a coma, cardiorespiratory support with intubation, as well as maintenance of airway, pulse, and blood pressure is the proper initial management.

**Pathophysiology**

Narcotic-induced leukoencephalopathy cannot be explained by a purely hypoxic insult alone, as primary hypoxia preferentially damages gray matter structures, a pattern that was not seen in our case. Furthermore, involvement of the corpus callosum argues against a purely hypoxic injury, as it is richly supplied with oxygen by plentiful perforating arterioles. Histopathological examinations of the brains of these types of patients demon-
effacement of the fourth ventricle, and upward bowing of the tentorium, complete edema producing mass effect on the brainstem (large arrow). A case requiring shunt placement was also described by Mills in 2008. In his report, Mills described the case of a 3-year-old girl who accidentally ingested methadone and whose MRI demonstrated bilateral cerebral and cerebellar edema with restricted diffusion in the white matter. All of these studies repeatedly demonstrate symmetric, abnormal white matter signal, with more recent studies documenting restricted diffusion in the white matter as well.

**Cerebellar Involvement**

Cerebellar involvement has been described in many papers discussing heroin-induced leukoencephalopathy. Morphine has an affinity for mu receptors with weak binding to delta and kappa receptors. Studies on these receptors have demonstrated that the cerebellar and limbic system have the greatest density of opioid receptors, although with a variable expression. The cerebellum is believed to have a predominance of mu receptors and, to a lesser degree, delta receptors, with no kappa receptors. It is postulated that the stimulation of these receptors can lead to a state of cellular energy depletion and that hypoxia and/or acidosis may enhance this effect. This theory is further corroborated by MR spectroscopy findings reported elsewhere that reveal results consistent with axonal injury without demyelination, with a lactate peak likely related to mitochondrial dysfunction. A condition described as ultra-rapid metabolism of codeine to morphine exists, which has contributed to fatal overdoses, including one involving a nursing infant through the mother’s breast milk. The etiology is related to the CYP2D6 ultra-rapid metabolism genotype and phenotype.

It is important to recognize the presence of acute cerebellitis related to opioid overdose. The cerebellum may not be very edematous, and hydrocephalus may not be present on the initial radiological studies. Significant cerebellar edema can develop within hours, and serial clinical and radiological evaluations may be needed. Given that these patients are often comatose with a compromised neurological examination, we recommend routine serial CT scanning, especially in the first 48 hours. An MR image should be obtained as soon as clinically feasible.

In some instances, regardless of etiology, acute cerebellitis may require neurosurgical intervention including CSF drainage and/or posterior fossa decompression. We advocate immediate ventriculostomy in cases of opioid-induced cerebellitis with hydrocephalus. Given the usual temporary nature of the hydrocephalus, we do not advocate placement of a shunt in the acute setting, although it
may be required in the long term. There is a risk of upward transtentorial herniation related to ventriculostomy; therefore, we suggest a gradual reduction of intracranial pressure, titrated on clinical response. This technique has been used in other cases of acute cerebellar edema. In 2001, Hamada et al. reported a case of acute cerebellitis in a 7-year-old boy successfully treated with steroids and CSF drainage via an external ventricular drain. In 1979, Asenbauer et al. successfully treated a child with acute parainfectious cerebellar swelling with ventriculostomy and posterior fossa decompression.

We do not advocate routine neurosurgical intervention, as the natural history of acute narcotic encephalopathy varies from case to case. If indicated, the timing of neurosurgical treatment should be based on serial clinical and radiological findings. We believe that an absolute indication to intervene is progressive cerebellar edema/stroke, especially if there is newly developed hydrocephalus and brainstem compression, as documented in the case presented in this report.

With the incidence of opioid overdose in children increasing, neurosurgeons need to be aware of the clinical and neuroimaging findings of opioid-induced acute leukoencephalopathy. In situations of opioid-induced cerebellitis leading to acute obstructive hydrocephalus, prompt diagnosis and timely surgical intervention are the keys to successful management. Surgical management includes ventriculostomy placement and, if needed, posterior fossa decompression. This case, to our knowledge, is the first report of surgical decompression used to treat cerebellar edema associated with opioid overdose in a child.

References


Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Reisner, Hayes, Holland, Kebriaei, Geller, Chern. Acquisition of data: Reisner, Hayes, Holland, Chern. Analysis and interpretation of data: Holland, Baum, Chern. Drafting the article: all authors. Critically revising the article: Reisner, Hayes, Wrubel, Kebriaei, Geller, Baum, Chern. Reviewed submitted version of manuscript: Reisner, Hayes, Wrubel, Geller, Chern. Approved the final version of the manuscript on behalf of all authors: Reisner. Study supervision: Reisner.

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