Clinical and radiologic features of pediatric opioid use-associated neurotoxicity with cerebellar edema (POUNCE) syndrome

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Case

A 20-month-old boy weighing 15 kg underwent a successful surgery for hypospadias under general anesthesia. Before discharge, he was given a 2 mg dose of oral morphine. His parents reportedly administered a 3 mg dose of oral morphine at home 2 hours later. Three hours later, he appeared drowsy and was put to bed. The next morning, approximately 14 hours later, he was not arousable and the ambulance was called. His oxygen saturation was at 94%, blood pressure at 90/60, and had decreased level of consciousness with poor respiratory effort. His blood venous gas showed pH = 6.91, PCO₂ = 115 mm Hg, PO₂ = 21 mm Hg, and bicarbonate of 22 mmol/L. He had pinpoint pupils and abnormal dystonic posturing. He was given naloxone 0.15 mg twice, 1 hour apart, with no effect, and he was then intubated.

The concentration of oral morphine was measured in the laboratory as 9.1 mg/mL (labeled as 10 mg/mL). His blood opiate concentration was 4.0 ng/mL, drawn 24 hours after his last dose of morphine, indicating that he was likely in the toxic range. We speculate that the child may have accidently received a higher dose than stated.

An MRI of the head that day showed dramatic findings including symmetric bilateral edema of the cerebellum and occipital lobes (figure, A–F) explaining his persistent decreased level of consciousness despite naloxone. He was brought into the operating room for posterior fossa craniectomy. He was extubated after a week and was discharged to the inpatient rehabilitation after 2 months with severe dysmetria, truncal ataxia, and cortical blindness. A repeat head MRI 1 year later demonstrated encephalomalacic changes involving the bilateral cerebellar and cerebral hemispheres (figure, G–J).

On follow-up 5 years later, he no longer had truncal ataxia or dysmetria. He can independently walk, run, and jump without falls. His cortical visual impairment has improved substantially, and a manifest left strabismus is noted in primary gaze. He has poor impulse control and becomes aggressive in stimulus-sensitive settings. He is fully conversational in 2 languages, but his vocabulary remains constrained.

Discussion

These MRI findings were consistent with a syndrome associated with opioid overdose increasingly recognized in pediatric patients with dramatic bilateral cerebellar involvement, which we have termed pediatric opioid use-associated neurotoxicity with cerebellar edema (POUNCE) syndrome (figure). Clinicoradiological monitoring is required for complications such as herniation, compression, and...
hydrocephalus secondary to cerebellar edema and may require external ventricular drains, posterior fossa decompression, and/or cerebellec-tomy. Features of the previously reported pediatric cases with opioid-exposure and bilateral cerebellar abnormalities are summarized (see table e-1, https://doi.org/10.5061/dryad.dfn2z34wh).

Similar MRI findings were described in the cases of ketamine and tricyclic antidepressant toxicities (table e-2, https://doi.org/10.5061/dryad.dfn2z34wh), which may be because of the cross-activation of opioid receptors or similar downstream factors. Adult cases exist with bilateral cerebellar edema after opioid use,1,2 and imaging similarities with adult cases of chasing-the-dragon leukoencephalopathy in inhaled heroin use3 increases the hypothesis that POUNCE syndrome is a pediatric manifestation of a similar pathophysiologic spectrum as these cases. In adults and older adolescents, opioid toxicity is more classically described with confluent bilateral periventricular and centrum semiovale leukoencephalopathy.

Some reports of delayed movement disorders4 after opioid exposure could be because of the delayed effects of hypoxic encephalopathy than direct toxicity because neuroimaging in these cases may show predilection or involvement of deep gray nuclei more consistent with the former entity.5

POUNCE does not seem to be explained by the differences of the opioid metabolism or blood-brain permeability between non-neonatal children and adults.6 Because it can occur with either morphine or fentanyl (Table e-1; https://doi.org/10.5061/dryad.dfn2z34wh), toxicity because of a specific metabolite such as morphine-3-glucuronide is unlikely. This may suggest that differences in the opioid-receptor factors such as binding affinity or capacity7 are why this occurs in children.

As the radiologic findings in POUNCE significantly differ from hypoxic-ischemic encephalopathy, a direct neurotoxic effect leading to cytotoxic edema is likely. Opioid-induced toxicity may lead to oligodendrocyte toxicity and
demyelination, increased blood-brain barrier permeability and edema, and neuronal damage through mitochondrial insult and apoptotic upregulation. Because most cases describe respiratory depression and no cases exist in patients with adequate respiratory support in the surgical and critical care setting, associated hypoxia and acidosis likely play an important pathogenetic role, potentially through exacerbating the mitochondrial oxidation-reduction pathways.

Despite significant structural damage, the clinical outcome was remarkable, demonstrating compensation through neuroplasticity. Although opioid overdose remains a significant public health concern, data on how it affects young children are lacking. Because most previous cases involved accidental ingestion in children, recognition of POUNCE is paramount in guiding clinicians to provide a diagnosis for patients and families.

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Appendix Authors

| Name                  | Location                          | Contribution                        |
|-----------------------|-----------------------------------|-------------------------------------|
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| Asuri Narayan Prasad, MBBS, MD, FRCPC, FRCPEdin | Western University, London, ON, Canada | Critical revision and study supervision |

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