Methadone-induced Toxic Encephalopathy In Pediatric Patients: Two Case Reports

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ABSTRACT

Toxic encephalopathy is a wide spectrum of encephalopathy secondary to insult from toxic substances, with variable clinical presentations from minor cognitive impairment to severe neurological dysfunction and death. Methadone-induced toxic encephalopathy is an extremely rare form of toxic encephalopathy which typically demonstrates abnormal imaging findings in the dentate nuclei or cerebellum. This is a report of methadone-induced toxic encephalopathy in two toddlers secondary to accidental ingestion. They were brought in unconscious to the emergency department of a tertiary hospital and were found to be cyanotic and pulseless, requiring cardiopulmonary resuscitation and mechanical ventilation. Magnetic resonance imaging (MRI) of the brain of both patients showed similar findings of symmetrical hyperintense foci in bilateral cerebellar hemispheres on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. These areas also demonstrated diffusion restriction on diffusion weighted imaging (DWI). Blood and urine toxicology results confirmed the presence of methadone in both patients. As the exact substance of accidental ingestion may not be known at the time of presentation, early radiological diagnosis of methadone-induced encephalopathy may prompt early initiation of treatment to prevent further life-threatening complications, particularly in vulnerable pediatric population.

CASE REPORT

Case 1
A 2-year-old female, whose father was on methadone replacement therapy, was found unconscious at home. She was brought in to the emergency department of a tertiary hospital. On examination, she was found to be cyanotic and pulseless. Her pupils were pinpoint and not reactive. Cardiopulmonary resuscitation and intubation were performed immediately with return of spontaneous circulation within 2 to 3 minutes after initiation of cardiopulmonary resuscitation. Her capillary blood gas showed severe mixed respiratory and metabolic acidosis. She was placed on mechanical ventilation and sedated with intravenous Morphine and Midazolam infusion. She was paralyzed with intravenous Rocuronium infusion and was started on whole body cooling therapy for 48 hours. In view of acute cardiopulmonary collapse, magnetic resonance imaging (MRI) of the brain was performed on day 3 of
admission. There were punctate symmetrical hyperintense foci in the cortices of bilateral cerebellar hemispheres on T2-weighted and FLAIR sequences (Figures 1 and 2). These areas of abnormal signal intensity demonstrated restricted diffusion (Figure 3). No focal signal abnormality was demonstrated in cerebral hemispheres or brainstem. She was extubated successfully on day 4 of admission. Upon cessation of sedation and paralysis, she gradually regained consciousness. Blood and urine toxicology results demonstrated the presence of Methadone (0.17 mcg/ml). She was eventually discharged well with no complication.

Case 2
A 3-year-old male, sibling of the aforementioned patient, was brought in together to the emergency department with similar presentation. He was found to be pulseless with no spontaneous respiration. His pupils were pinpoint and non-reactive. Cardiopulmonary resuscitation and intubation were performed immediately. Return of spontaneous circulation only occurred after 1 hour and 15 minutes of active resuscitation. His capillary blood gas showed severe mixed respiratory and metabolic acidosis with no electrolyte derangement. He was placed on mechanical ventilation and kept sedated with intravenous morphine and midazolam. He was also paralyzed with intravenous Rocuronium infusion and was put on whole-body cooling therapy for 48 hours. In view of acute cardiopulmonary collapse, MRI of the brain was performed on day 4 of admission. There were symmetrical patchy hyperintense areas in the cortical region of bilateral cerebellar hemispheres on T2-weighted and FLAIR sequences (Figures 4 and 5). These areas also demonstrated restricted diffusion (Figure 6). These findings were similar but more extensive compared to that of his sibling. He was extubated successfully on day 4 of admission. His blood and urine toxicology results showed the presence of Methadone (0.05 mcg/ml). He recovered well in the ward and was eventually discharged well with no complication.

DISCUSSION
Toxic encephalopathy is a wide spectrum of encephalopathy as a result of toxic substance. The clinical features of toxic encephalopathy may be variable, ranging from minor cognitive impairment to severe neurological dysfunction, including muscle spasms, hemiparesis, dysarthria, ataxia, dementia, stupor, coma and death (1).

There are numerous agents that can contribute to toxic encephalopathy; these include chemotherapy or immunosuppressive therapy, environmental toxins, drug of abuse or infectious in origin (1). In a retrospective review of 101 patients, Özütemiz et al. found that chemotherapy is the most common cause, followed by opioids, acute hepatic encephalopathy, and immunosuppressants, while the cause was unknown in 7% (2). Most of the available literature describe the neurotoxic changes induced by heroin, which is an opioid made from morphine (3). The neurologic sequelae of opiate intoxication and overdose are multiple, including brain injury from primary neurotoxicity and secondary hypoxia/anoxia (4). The direct neurotoxic effects of opiates in adults are well documented in the medical literature. In contrast, there is a paucity of information regarding the neurological effects of prescription opioid overdose in children. Abnormal neurologic examination findings were universally described, which include altered consciousness, bradypnea, miotic pupils, hyperreflexia and/or hypertonia, and ataxia (4).

Opioid-related toxic encephalopathy has been reported to show extensive and symmetrical abnormal signal intensity in the deep white matter of both cerebral hemispheres, with sparing of the subcortical U-fibres (3). These affected areas showed high signal intensity on diffusion-weighted imaging without corresponding hypointensity on apparent diffusion coefficient maps (3). Morales et al. reported a case of post-opioid toxic encephalopathy showing non-vascular distribution of diffusion positive lesions in both cerebellar hemispheres and globus pallidus with preserved cerebral perfusion on MRI (5). Acute toxic encephalopathy with reduced diffusion may be clinically reversible and radiologically reversible on DWI, and may also be reversible, but to lesser degree on FLAIR imaging (6).

We report two cases of methadone-induced toxic encephalopathy, both demonstrating similar appearance on MRI. There was symmetrical signal abnormality in bilateral cerebellar cortices, seen as high signal intensity on T2-weighted (Figures 1, 2 and 4) and FLAIR (Figure 5) sequences, with restricted diffusion (Figures 3 and 6). The patients had cardiopulmonary arrest for a significant period of time which makes hypoxic-ischemic injury an important differential diagnosis. In moderate-to-severe cases of hypoxic-ischemic encephalopathy (HIE), vulnerable areas are the perirolandic and occipital cortices. In more severe cases of HIE, the effects may cause oedema of the entire cerebral cortex and eventually become necrotic (7). There was no signal abnormality seen in the supratentorial brain in these two patients. Toxicology screening from urine and serum samples of these two patients revealed high amounts of methadone. Therefore, the imaging findings along with the toxicology results are strongly suggestive of methadone-induced toxic encephalopathy.

Etiology & Demographics:
Methadone is a synthetic, long-acting opioid with high affinity for the mu class of opioid receptors which are predominantly found in the cerebellum and limbic system in humans (8, 9). It is used in the treatment of opiate dependence and detoxification and for patients with severe chronic pain. Acute intoxication can be lethal. The incidence of methadone-induced toxic encephalopathy is extremely rare in pediatric population as literature search revealed limited cases of methadone-induced neurotoxicity (3, 8, 10, 11). Those who are at risk include children who are prescribed opioids, exposed to opioids in utero and through breast milk or due to accidental ingestion.
Imaging Findings:
High affinity of methadone for the mu class opioid receptors which are predominantly found in the cerebellum and limbic system results in the imaging findings of symmetrical involvement of dentate nuclei or cerebellum with hyperintensity on T2-weighted and FLAIR sequences (11). Diffusion restriction may or may not be present (12).

Diffuse cerebellar swelling, hydrocephalus and bilateral lesions in the hippocampi were previously reported in pediatric patients with opioid toxicity (8, 11, 13). Watershed infarcts in bilateral cerebellum were also reported in one case, probably related to hypoperfusion exacerbated by respiratory depression (13). Delayed MRI findings of signal abnormalities in temporomesial regions, basal ganglia and substantia nigra have been reported (10). Duran et al. described that restricted diffusion, albeit most marked in the cerebellum in the cases of opioid overdose in children, was also present in watershed areas of the deep white matter, where circulatory redundancy between the anterior and posterior circulation is minimal (4).

Treatment & Prognosis:
Most of the morbidity and mortality related to opioid use occur after acute ingestion. Hypoxia, anaphylaxis, pulmonary edema, acute respiratory acidosis and aspiration pneumonitis are known life-threatening complications. Dose of 1 mg/kg can lead to serious apnea and death (14). These medical emergencies require urgent attention (15). Priorities in management include assessment and establishment of effective ventilation and oxygenation, followed by hemodynamic support and administration of an opioid antagonist. Naloxone is an important antidote for the reversal of opioid-induced respiratory and central nervous system depression which can be administered via intravenous, intramuscular, subcutaneous or endotracheal routes. As the duration of naloxone’s activity is shorter than that of most opioids, the drug may need to be administered repeatedly or continuously (15). The prognosis depends on clinical presentation of patients which can range from non-specific symptoms to severely unwell patients requiring resuscitation.

Differential Diagnoses:
A. Infective cerebellitis
Infective cerebellitis is characterized by isolated inflammation of cerebellum usually caused by viral agents such as Varicella zoster, Epstein barr and measles. Other infective agents include tuberculosis and neurocysticercosis. The imaging findings are usually unremarkable. However, in severe cases it can demonstrate diffuse swelling of bilateral cerebellar hemispheres involving both grey and white matter, mild diffusion restriction and contrast enhancement of the cerebellar cortex and leptomeninges. Unilateral involvement of cerebellum is uncommon, and involvement of vermis and cerebellar peduncles is variable (12). Parenchymal granulomas like tuberculomas and neurocysticercosis can also occur in the cerebellum (12).

B. Autoimmune disease
Autoimmune encephalitis as a cause for encephalopathy in pediatric patients is becoming more common. It may be triggered by an infection, vaccine, or occult neoplasm. Autoantibodies are directed against intracellular neuronal antigens and resulting in encephalitis. MRI demonstrates FLAIR or T2-weighted hyperintensities in the bilateral temporal lobes, brainstem or, in some cases, subcortical regions and cerebellum with variable gadolinium enhancement (16).

C. Hypoxic-ischemic insult
Mild to moderate global ischemic insults to the brain in young children usually result in watershed zone infarcts. Severe hypoxic-ischemic insult in young children primarily affects the gray matter structures: the basal ganglia, thalami, cerebral cortex, cerebellum, and hippocampi. Diffusion-weighted MR imaging is the earliest imaging modality to be positive, usually within the first few hours after a hypoxic-ischemic event (17). During the first 24 hours, diffusion-weighted imaging may demonstrate increased signal intensity in the cerebellar hemispheres, basal ganglia, or cerebral cortex (in particular, the perirolandic and occipital cortices) (18). The thalami, brainstem, or hippocampi may also be involved (18, 19). Conventional T1- and T2-weighted images are often normal or demonstrate only very subtle abnormalities. In the early subsacute period (24 hours–2 weeks), conventional T2-weighted images typically become positive and demonstrate increased signal intensity and swelling of the injured gray matter structures, although these findings may be subtle. In the chronic stage, T2-weighted images may demonstrate some residual hyperintensity in the basal ganglia, and T1-weighted images may show areas of high signal intensity in the cortex, which represent cortical necrosis (17).

D. Demyelinating disorders
Acute disseminated encephalomyelitis, multiple sclerosis and progressive multifocal encephalopathy are among the examples of demyelinating disorders which may involve the cerebellum. On MRI, demyelinating disorders demonstrate T2-weighted or FLAIR hyperintensities which can be small punctate lesions or large tumefactive lesions. They show variable enhancement pattern with open ring enhancement along the leading edge of inflammation being the most characteristic pattern (16).

E. Posterior reversible encephalopathy syndrome (PRES)
Posterior reversible encephalopathy syndrome (PRES) is a cliniconeuroradiological disease entity, which is associated with various medical conditions in children with hematologic and malignant disease including leukemia, solid tumors, aplastic anemia, and autoimmune disease. It is represented by characteristic magnetic resonance imaging findings of subcortical/cortical hyperintensity in T2-weighted sequences. It is more often seen in parietaloccipital lobes and is accompanied by clinical neurological changes. Typical transient lesions on MRI (i.e., edema of the subcortical white matter shown on T2 weighted images and fluid attenuation...
inversion recovery (FLAIR) images) are pathognomonic of the syndrome (20). In addition, PRES can affect basal ganglia, cerebellar hemispheres, and brainstem (21).

TEACHING POINT

Methadone-induced encephalopathy typically demonstrates symmetrical hyperintensity on conventional T2-weighted and FLAIR sequences involving the dentate nuclei or cerebellum with or without the presence of diffusion restriction. This is due to the high affinity of methadone for the mu class opioid receptors which are predominantly found in the cerebellum and limbic system. Knowledge on the imaging findings and potential complications of methadone-induced leukoencephalopathy is important as acute methadone intoxication can be life-threatening in vulnerable pediatric patients. Early diagnosis on imaging may prompt early treatment to prevent further life-threatening complications.

REFERENCES

Figure 1: 2-year-old female with methadone-induced encephalopathy
FINDINGS: Axial non-contrast MRI of the brain, T2W sequence, from superior to inferior (A to C) demonstrates punctate symmetrical hyperintense foci in the cortices of bilateral cerebellar hemispheres (white arrows).
TECHNIQUE: Siemens Skyra MRI scanner. Magnetic strength = 3.0 Tesla. No intravenous contrast was administered.

Figure 2: 2-year-old female with methadone-induced encephalopathy
FINDINGS: Coronal non-contrast MRI of the brain, FLAIR sequence, from anterior to posterior (A to B) demonstrates punctate symmetrical hyperintense foci in the cortices of bilateral cerebellar hemispheres (white arrows).
TECHNIQUE: Siemens Skyra MRI scanner. Magnetic strength = 3.0 Tesla. No intravenous contrast was administered.
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**Figure 3**: 2-year-old female with methadone-induced encephalopathy

**FINDINGS**: Axial non-contrast MRI of the brain, DWI (A to B) and ADC (C to D) sequences from superior to inferior, demonstrates punctate symmetrical foci of restricted diffusion in the cortices of bilateral cerebellar hemispheres (white arrows).  
**TECHNIQUE**: GE Healthcare Signa HDxt MRI scanner. Magnetic strength = 1.5 Tesla. No intravenous contrast was administered.

**Figure 4**: 3-year-old male with methadone-induced encephalopathy

**FINDINGS**: Axial non-contrast MRI of the brain, T2W sequence, from superior to inferior (A to C) demonstrates symmetrical patchy hyperintense areas in the cortical region of bilateral cerebellar hemispheres (white arrows).  
**TECHNIQUE**: GE Healthcare Signa HDxt MRI scanner. Magnetic strength = 1.5 Tesla. No intravenous contrast was administered.
Figure 5: 3-year-old male with methadone-induced encephalopathy
FINDINGS: Coronal non-contrast MRI of the brain, T2W sequence from anterior to posterior (A to D), demonstrates symmetrical patchy hyperintense areas in the cortical region of bilateral cerebellar hemispheres (white arrows).
TECHNIQUE: GE Healthcare Signa HDxt MRI scanner. Magnetic strength = 1.5 Tesla. No intravenous contrast was administered.
Aetiology | Methadone-induced toxic leukoencephalopathy is caused by acute intoxication by this synthetic, long-acting opioid with high affinity for the mu class of opioid receptors which are predominantly found in the cerebellum and limbic system in human.

Incidence | Unknown. Few reported cases of methadone-induced leukoencephalopathy in pediatric population were found on literature review.

Gender ratio | No

Age predilection | No

Risk factors | Children who are prescribed opioids, exposed to opioids in utero and through breast milk or accidental ingestion.

Treatment | Assessment and establishment of effective ventilation and oxygenation, followed by hemodynamic support and the administration of an opioid antagonist (Naloxone).

Prognosis | Variable, depending on clinical presentation and severity of insult. Toxic encephalopathy may be clinically and radiographically reversible.

Findings on imaging | Symmetric involvement of dentate nuclei or cerebellum with hyperintensity on T2-weighted and FLAIR sequences. There can be presence or absence of diffusion restriction.

Table 1: Summary table of key aspects of methadone-induced encephalopathy.
<table>
<thead>
<tr>
<th>Entity</th>
<th>Magnetic Resonance Imaging</th>
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<tbody>
<tr>
<td>Toxic/Metabolic diseases</td>
<td>• Symmetrical involvement of dentate nuclei or cerebellum</td>
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<td></td>
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<td></td>
<td>• With or without diffusion restriction</td>
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<td></td>
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<td></td>
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</tr>
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<td>Infective cerebellitis</td>
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<td>• Mild diffusion restriction and contrast enhancement in the involved cerebellar cortex and leptomeninges.</td>
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<td>• Parenchymal granulomas like tuberculomas and neurocysticercosis can occur in the cerebellum as in other areas of the brain.</td>
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<td>Autoimmune disease</td>
<td>• FLAIR or T2-weighted hyperintensities in medial temporal lobes, brainstem or, in some cases, subcortical regions, and cerebellum may be present.</td>
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<td>• Variable Gadolinium enhancement.</td>
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<td>• Lesions may be non-enhancing or may show open ring type of enhancement along the leading edge of inflammation.</td>
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<td>Posterior reversible encephalopathy syndrome</td>
<td>• Subcortical/cortical hyperintensity in T2-weighted sequences.</td>
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<td>• More often seen in parieto-occipital lobes.</td>
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<td>• Typical transient lesions on MRI (i.e., edema of the subcortical white matter shown on T2 weighted images and fluid attenuation inversion recovery (FLAIR) images) are pathognomonic.</td>
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<td>• Can affect basal ganglia, cerebellar hemispheres, and brainstem.</td>
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Table 2: Differential diagnoses table for methadone-induced encephalopathy.

**ABBREVIATIONS**

ADC = Apparent diffusion coefficient  
DWI = Diffusion weighted imaging  
FLAIR = Fluid-attenuated inversion recovery  
HIE = Hypoxic-ischemic encephalopathy  
MRI = Magnetic resonance imaging  
PRES = Posterior reversible encephalopathy syndrome

**KEYWORDS**

Methadone; encephalopathy; cerebellitis; pediatrics; magnetic resonance imaging

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