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CLINICAL REPORT

Dextromethorphan Associated Neurotoxicity with Cerebellar Edema (DANCE) Syndrome in Young Children: Neuroimaging Features

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ABSTRACT

Dextromethorphan toxicity in young children (especially those with age 4 years or younger) can have an extremely poor prognosis if untreated. However, if timely recognized and optimally managed, it can have a good clinical outcome despite significant initial insult. We present 3 pediatric cases (< 5 years old) with sudden unresponsiveness following ingestion of cough medications containing dextromethorphan. All these children showed cytotoxic edema in cerebellar hemispheres on MR brain, with diffusion restricting foci in supratentorial white matter in 2 patients. These features resemble the recently described acute opioid toxidrome in children, the POUNCE syndrome (Pediatric Opioid Use-associated Neurotoxicity with Cerebellar Edema). Hence, we name this entity "DANCE" (Dextromethorphan Associated Neurotoxicity with Cerebellar Edema) to increase the awareness of dextromethorphan toxicity in young children and the need to promptly recognize it to initiate optimal management.

Keywords: POUNCE syndrome, Pediatric Opioid Use-associated Neurotoxicity with Cerebellar Edema, DANCE syndrome, Dextromethorphan Associated Neurotoxicity with Cerebellar Edema, dextromethorphan toxicity

ABBREVIATIONS: POUNCE= Pediatric Opioid Use-associated Neurotoxicity with Cerebellar Edema; DANCE= Dextromethorphan Associated Neurotoxicity with Cerebellar Edema.

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INTRODUCTION

Dextromethorphan associated neurotoxicity in young children is less well described in Literature. "POUNCE" syndrome, the term used for "pediatric opioid use-associated neurotoxicity with cerebellar edema", is a recently recognized clinico-radiological entity in children occurring secondary to acute opioid toxicity. It is extremely rare with fewer than 20 cases published in literature.[1] We report 3 pediatric cases (< 5 years old) who presented to our institution over a span of 2 years with clinical and radiological features like POUNCE syndrome, but with an antecedent history of ingestion of over-the-counter cough medications containing "dextromethorphan" for fever, cough and coryza. We therefore name this entity as "DANCE" (Dextromethorphan Associated Neurotoxicity with Cerebellar Edema) syndrome due to its striking resemblance with POUNCE syndrome. We consider it different from POUNCE syndrome as it did not occur directly due to opioid ingestion, rather occurred secondary to ingestion of an opioid analogue with a slightly different mechanism of action. Our intention is to increase awareness of this entity in young children with age of 4 years or less, in whom over-the-counter antitussive medications containing dextromethorphan are otherwise not recommended but are still used in few parts of the world.

Case Series

Clinical Presentation

Case 1: A 4-year-old girl presented with complaints of low-grade fever, cough, and coryza for two days. She was given a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1mg/kg), chlorpheniramine maleate and phenylephrine hydrochloride from a local physician. Three hours after ingestion of the cough syrup, she presented with sudden unresponsiveness. A similar presentation was elicited at the same time in her younger sibling of 2-years-age, who succumbed to death before reaching hospital. There was no history of any animal bites, exposure to other toxins like organophosphorus compounds or opioids. At arrival, the child was unconscious with a Glasgow coma scale (GCS) of E1V1M2 and had bilateral pinpoint pupils. She was febrile, tachycardic, had an elevated blood pressure of 131/67 mmHg, low oxygen saturation of 75% at room air, and a low blood glucose level of 43 mg/dl. Examination revealed generalized hypotonia with brisk deep tendon reflexes and bilateral extensor plantar.

Case 2: A 2-year-old-boy presented with complaints of fever and upper respiratory tract illness for one day, for which a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1.6 mg/kg) was prescribed in a local clinic. After one hour of ingestion of the syrup, the child was found to be unresponsive. On the way to the hospital, he had seven brief episodes of generalized tonic-

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clonic seizures, each lasting for 3-5 minutes. On arrival, the child was unconscious , febrile, had tachycardia, bilateral pinpoint pupils and generalized hypotonia with brisk deep tendon reflexes and bilateral extensor plantar.

Case 3: A 1.5-year-old girl presented with intermittent fever and dry cough for two to three days and decreased responsiveness for the last 2 hours. She had an episode of abnormal body movements in the form of clenching of teeth and frothing from mouth, with bluish discoloration of the body one hour before reaching our hospital. She was given a similar oral cough syrup containing dextromethorphan hydrobromide as the previous two patients at a local private hospital for her respiratory illness. On examination, the child was lethargic (GCS: E1V2M4) and had bilateral constricted pupils. She developed respiratory failure with a SpO2 of 54% at room air and was found to have hypoglycemia.

All the children had negative infectious disease workup and normal CSF examination. Patient 1 had positive IgG antibodies for COVID-19. Hematological and biochemical investigations revealed elevated transaminases [AST/ ALT (IU/L) in patient 1: 56/197, patient 2: 118/41 and patient 3: 128.9/43.9]. Patient 3 had raised Creatine kinase–MB (CKMB) (61.4) and CKNAC (1095) with hyperkalemia, indicating rhabdomyolysis. She also had a high IL-6 value of 133 pg/ml (normal value: <4.4).

Imaging Findings

After initial resuscitation, the patients underwent MRI brain within six hours of their presentation. MRI brain in all the patients consistently showed confluent T2/FLAIR hyperintensities in bilateral cerebellar hemispheres with restricted diffusion on corresponding DWI sequence, suggestive of cytotoxic edema. Multiple other punctate and linear foci of restricted diffusion were seen in bilateral centrum semiovale and corona radiata in patient 1 and 2. **(Figure 1 and Figure 2)** Patient 3 did not have supratentorial involvement. Basal ganglia or hippocampi were not involved except in patient 2 where few diffusion restricting foci were seen in left caudate nucleus, and bilateral posterior putamina. **(Figure 2)** None of the patients showed cerebral cortical involvement, blooming/ bleeds on SWI, enhancement on post contrast T1W sequences or any evidence of vascular stenosis/ occlusion on TOF MR angiography. These features strongly resembled the recently described typical features of POUNCE syndrome.[1]

Treatment and follow up

Emergent measures were taken in all the children by securing the airway with intubation and administering 10% dextrose bolus for hypoglycemia. Considering dextromethorphan-induced encephalopathy, they were given bolus doses of Naloxone followed by an infusion for 48 hours along with measures to reduce intracranial pressure. In view of cerebellar edema, they were given methylprednisolone pulse therapy for five days, followed by oral prednisolone for two weeks. All the children showed dramatic improvement in sensorium after methylprednisolone therapy. They were discharged in stable condition without any residual deficits after a brief hospital stay varying from five to ten days and had a normal neurological examination on a 2 week follow up. Follow up MR done 2 weeks later in patient 3 showed significant resolution of T2/FLAIR hyperintensities in cerebellum with normalization of restricted diffusion. **(Figure 3) Online supplemental data** summarizes the clinical and imaging features, treatment, and follow up of the patients in the clinical report.

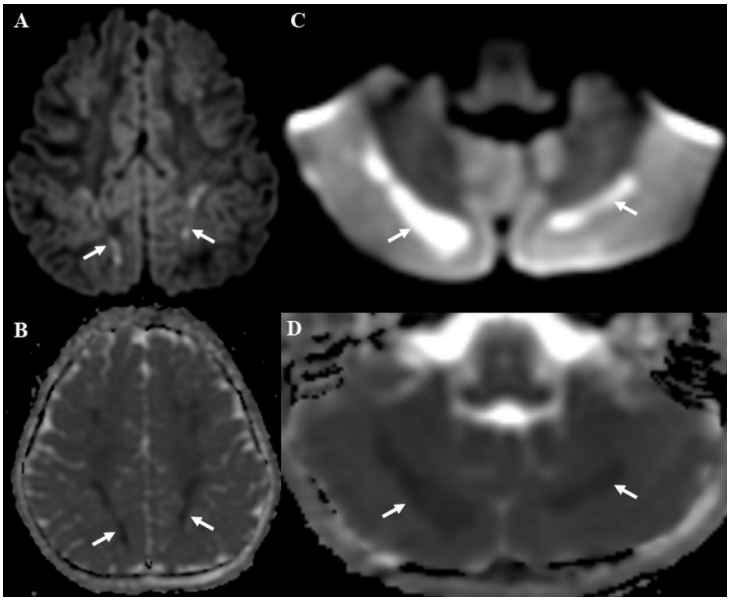

FIG 1: Image of a 4-year-old girl who presented with sudden unresponsiveness and pinpoint pupils three hours following ingestion of a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1mg/kg), prescribed to her for complains of low-grade fever, cough, and coryza from an outside hospital. Axial MR brain images [diffusion weighted images (A and C) and their corresponding ADC maps (B and D)] show near symmetrical linear diffusion restricting foci in bilateral centrum semiovale (arrows in A and B). Symmetrical and confluent diffusion restricting areas are seen in bilateral cerebellar hemispheres (arrows in C and D), indicating cerebellar edema. These imaging features are termed DANCE (Dextromethorphan Associated Neurotoxicity with Cerebellar Edema) syndrome in young children.

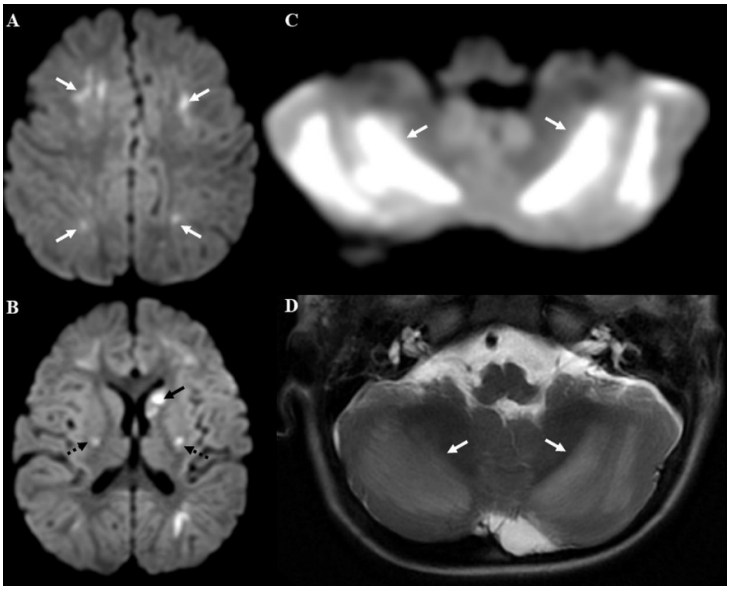

FIG 2. Image of a 2-year-old boy who presented with unresponsiveness, brief episodes of generalized tonic-clonic seizures and bilateral pinpoint pupils one hour following ingestion of a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1.6 mg/kg), prescribed to him for upper respiratory tract illness. Axial MR brain images (A, B, C: Diffusion weighted sequence and D: T2 weighted sequence) show features of DANCE syndrome. Symmetrical linear diffusion restricting foci with corresponding low values on ADC map (not shown) are seen in bilateral centrum semiovale (arrows in A) and deep white matter (B). Few diffusion restricting foci are seen in left caudate nucleus (black solid arrow in B) and bilateral posterior putamina (black dashed arrows in B). Confluent areas of diffusion restriction (with low values on ADC map: not shown) are seen in bilateral cerebellar hemispheres (arrows in C), with corresponding hyperintense signal on T2W images.

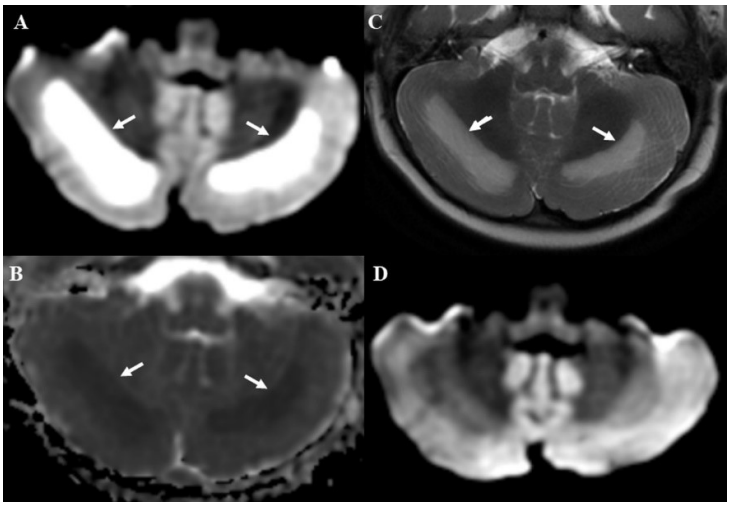

FIG 3. Image of a 1.5-year-old girl who ingested oral cough syrup containing dextromethorphan hydrobromide for intermittent fever and dry cough and now presented with decreased responsiveness, a seizure episode and bilateral constricted pupils. Axial MR brain images (A: Diffusion weighted sequence, B: ADC map, C: T2W sequence) show features of DANCE syndrome. Symmetrical and confluent areas of restricted diffusion (arrows in A) with low values on ADC map (arrows in B) and corresponding hyperintense signal on T2W sequence (arrows in C) are seen in bilateral cerebellar hemispheres, indicating cerebellar edema. No diffusion restricting foci were seen in supratentorial white matter in this case (not shown). D. Follow up MR image (diffusion weighted sequence) done 2 weeks later in the patient shows no residual diffusion restriction in cerebellum.

DISCUSSION

Dextromethorphan associated neurotoxicity in young children is a less known entity. We present three pediatric patients who presented with significant neurological deterioration after ingestion of over-the-counter anti-tussive medications containing "dextromethorphan" for their short febrile respiratory illness. The patients in our series had strikingly similar clinical features and MRI brain appearances to the recently described "POUNCE" syndrome[1].

"POUNCE" syndrome is a term coined by Kim et al. for a distinct clinico-radiological syndrome caused by acute opioid toxicity in children. It is characterized by cerebellar edema in the form of T2/FLAIR hyperintensities with or without restricted diffusion. It is often accompanied by some degree of supratentorial white matter injury predominantly in deep and periventricular white matter, seen as punctate or confluent T2/FLAIR hyperintensities which may show restricted diffusion in early stages.[1] Few of the previously published reports on pediatric opioid toxicity have also described similar cerebellar and white matter injury, often with malignant cerebellar edema leading to complications including cerebellar tonsillar herniation, compression of brainstem and rapidly evolving obstructive hydrocephalus. These complications may amount to dreaded consequences including death, if not addressed in early stages by anti-edema measures or posterior fossa decompression or external ventricular drainage tube placement, if necessary.[1-12]

All the children in our report presented with profound encephalopathy and respiratory failure and had cerebellar edema on MRI. Two of them showed supratentorial involvement. None of the cases showed hemorrhages or contrast enhancement, although hemorrhage has been reported in few of previously published cases of POUNCE.[6] Our patients did not show significant compression of the brainstem or upstream hydrocephalus and did not require surgical measures, likely due to early recognition and administration of appropriate therapy.

Dextromethorphan, an over-the-counter anti-tussive medication, is D-isomer of levorphanol, which is a synthetic analogue of codeine, an opioid receptor agonist. Its cough suppressant actions in regular doses are mediated via its action on sigma opioid receptors in medulla. Due to its stereochemistry, it does not bind to mu and delta opioid receptors, which are commonly involved in manifestations of opioid toxicity.[13,14]

Although a definite histopathological evidence is lacking till date, POUNCE is postulated to occur due to direct neurotoxic effects of the opioid agents on glial and neuronal cells with contribution from factors like apoptotic upregulation due to mitochondrial injury and potentiation of these mitochondrial pathways from anoxic insults secondary to respiratory depression.[1,2,4] Predominant cerebellar involvement in POUNCE is proposed due to abundance of mu receptors in cerebellum, which are the primary target for opioid toxicity.[1]

Although dextromethorphan primarily binds with sigma opioid receptors, due to a striking resemblance of clinical and radiological syndrome in all the cases of our series with POUNCE, we postulate the occurrence of "DANCE" syndrome in small children with dextromethorphan toxicity and propose a similar mechanism with possibility of cross reactivity with mu receptors. Over-the-counter cough remedies containing dextromethorphan have been largely prohibited for children less than 2 years and not recommended for use in those with less than 4 years of age.[14-16] The occurrence of DANCE syndrome in young children in our report further emphasize the necessity of this caution. A recently published case report has highlighted clinical features of opioid toxidrome secondary to dextromethorphan toxicity in children, but it is extremely rare and there is paucity of knowledge about the associated neuroimaging features.[17] Though never proven, occurrence of dextromethorphan toxicity in only young children may be due to enhanced sensitivity of receptors in this age group, leading to a heightened effect even at doses less than toxic range. Further research into this matter is warranted.

The fact that all the children in our series had a respiratory illness, showed good response to methylprednisolone, one of them had high IL6 levels and one had positive IgG for COVID-19, a possibility of an underlying para-infectious immunological phenomenon and the role of viral infection in increasing predisposition to DANCE syndrome also needs to be investigated. In this context, the most important differential of DANCE syndrome remains viral/ infectious cerebellitis. However, a specific MR pattern involving both cerebellum (in all the children) and supratentorial white matter (in two of the three), a remarkably similar clinical context with features including pinpoint pupils, striking resemblance to POUNCE syndrome, lack of contrast enhancement, and normal blood and CSF investigations despite extensive infectious disease workup make the diagnosis of an infectious/ viral cerebellitis less likely than DANCE. Hypoxic ischemic encephalopathy is another major clinical differential of DANCE syndrome in patients with sudden unresponsiveness and respiratory failure. Predominant involvement of cerebellum and deep white matter without cortical and basal ganglia edema on MRI brain makes the distinction possible from hypoxic ischemic encephalopathy, where cerebellum is usually late to be involved. [1,18, 19]

A similar predilection for cerebellum and white matter in cases of "Chasing the dragon" leukoencephalopathy occurring due to chronic rather than acute inhalation of heroin and recently described "Cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome" and "Opioid Associated Amnestic syndrome (OAS)" occurring secondary to acute opioid toxicity in adults suggest that all these disorders may represent continuum of similar pathophysiology.[18-21] Nevertheless, there are differences (**Online Supplemental Data)** between these entities possibly due to varying binding affinity of opioid receptors in different parts of the brain in children and adults.[22]

Our report has a few limitations. We could not determine the serum levels of dextromethorphan in the children in our series. The lack of supratentorial involvement in the third child in our study could not be explained. This may be related to difference in sensitivity of the brain receptors at different ages as the third child was the youngest of the three (less than two years of age), but we refrain from making a definite assumption without any histopathological or other conclusive evidence from literature. Due to logistic reasons, MR follow up was not available in two of the three patients. However, a normal neurological examination was reassuring, and pointed towards a definite clinical improvement in these patients.

DANCE syndrome can have an extremely poor prognosis if untreated as could be seen in sibling of case 1 who succumbed to death before reaching our hospital. However, if timely recognized and optimally managed, it can have a good clinical outcome despite significant initial insult as seen in all the patients of our series, likely owing to the neuroplasticity of pediatric brain.[1] This highlights the importance of early neuroimaging, need to promptly recognize the specific DANCE pattern and urgently treat this rare entity. The case series reiterates the adverse effects of dextromethorphan on young children and the need to monitor its use, especially in children less than 4 years of age.

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REFERENCES

1. Kim DD, Prasad AN. Clinical and radiologic features of pediatric opioid use-associated neurotoxicity with cerebellar edema (POUNCE) syndrome. *Neurology*. 2020;94:710–2. https://doi.org/10.1212/wnl.0000000000009293

2. Duran D, Messina RD, Beslow LA, et al. Malignant cerebellar edema subsequent to accidental prescription opioid intoxication in children. *Front Neurol*. 2017; 8:362. https://doi.org/10.3389%2Ffneur.2017.00362

3. Wheaton T, Toll BJ, Breznak K, et al. Opioid-induced toxic leukoencephalopathy: a case report and review of the literature. *Heliyon*. 2019;5:e03005. https://doi.org/10.1016/j.heliyon.2019.e03005

4. Chen CH, Mullen AJ, Hofstede D, et al. Malignant cerebellar edema in three-year-old girl following accidental opioid ingestion and fentanyl administration. *Neuroradiol J*. 2019 Oct;32:386-91. https://doi.org/10.1177/1971400919863713

5. Haut LN, Radhakrishnan R, Lutfi R, et al. Acute cytotoxic cerebellar edema subsequent to fentanyl patch intoxication in an infant. *Case Rep Crit Care*. 2021;2021:9449565. https://doi.org/10.1155/2021/9449565

6. Reisner A, Hayes LL, Holland CM, et al. Opioid overdose in a child: case report and discussion with emphasis on neurosurgical implications. *J Neurosurg: Pediatr*. 2015;16:752-7. https://doi.org/10.3171/2015.4.peds14667

7. Nanan R, Von Stockhausen HB, Petersen B, et al. Unusual pattern of leukoencephalopathy after morphine sulphate intoxication. *Neuroradiology*. 2000 Nov;42:845-8. https://doi.org/10.1007/s002340000442

8. Bellot B, Michel F, Thomachot L, et al. Acute leukoencephalopathy after buprenorphine intoxication in a 2-year-old child. *Eur J Paediatr neurol*. 2011;15:368-71. https://doi.org/10.1016/j.ejpn.2011.03.002

9. Haghighi-Morad M, Naseri Z, Jamshidi N, et al. Methadone-induced encephalopathy: a case series and literature review. *BMC Med Imaging*. 2020;20:1-9. https://doi.org/10.1186/s12880-020-0410-9

10. Tiong SC, Chieng JS, Khoo HW, et al. Methadone-induced toxic encephalopathy in pediatric patients: two case reports. *J Radiol Case Rep*. 2019;13:1-9. https://doi.org/10.3941%2Fjrcr.v13i5.3658

11. Mills F, MacLennan SC, Devile CJ, et al. Severe cerebellitis following methadone poisoning. *Pediatr Radiol*. 2008;38:227-9. https://doi.org/10.1007/s00247-007-0635-6

12. Rando J, Szari S, Kumar G, et al. Methadone overdose causing acute cerebellitis and multi-organ damage. *Am J Emerg Med*. 2015;34:343.e1-3. https://doi.org/10.1016/j.ajem.2015.06.032

13. Journey JD, Agrawal S, Stern E. Dextromethorphan Toxicity. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538502. Accessed August 2, 2024

14. Rosenbaum C, Boyer E W. Dextromethorphan misuse and poisoning: Clinical features and diagnosis. In: UpToDate, Connor RF (Ed), Wolters Kluwer. https://www.uptodate.com/contents/dextromethorphan-misuse-and-poisoning-clinical-features-and-diagnosis. Accessed December 28, 2023

15. AHFS Patient Medication Information [Internet]. Bethesda (MD): American Society of Health-System Pharmacists, Inc.; c2019. Dextromethorphan; [revised 2022 Jan 15; cited 2024 Aug 2]. https://medlineplus.gov/druginfo/meds/a682492.html. Accessed August 2, 2024

16. US Food and Drug Administration. Use caution when giving cough and cold products to kids. https://www.fda.gov/drugs/special-features/use-caution-when-giving-cough-and-cold-products-kids. Accessed August 2, 2024

17. Kumar D, Shinde V, Khuraijam S, et al. Two Cases of Dextromethorphan Overdose Reversed by Naloxone. *Cureus*. 2023 Feb 1;15(2): e34501. https://doi.org/10.7759/cureus.34501

18. Mallikarjun KS, Parsons MS, Nigogosyan Z, et al. Neuroimaging findings in CHANTER syndrome: a case series. *AJNR Am J Neuroradiol*. 2022;43:1136-41. https://doi.org/10.3174/ajnr.a7569

19. Jasne AS, Alsherbini KH, Smith MS, et al. Cerebellar hippocampal and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome. *Neurocrit Care*. 2019;31:288-96. https://doi.org/10.1007/s12028-018-00666-4

20. Atac MF, Vilanilam GK, Damalcheruvu PR, et al. Cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome in the setting of opioid and phencyclidine use. *Radiol Case Rep*. 2023;18(10):3496-500. https://doi.org/10.1016/j.radcr.2023.07.015

21. McConnell E, Bai J, McConnel E. Hippocampal and Cerebellar Involvement in Opioid-Associated Amnestic Syndrome: A Unique Case Report. *Cureus*. 2023;15: e44248. https://doi.org/10.7759%2Fcureus.44248

22. Zagon IS, Gibo DM, McLaughlin PJ. Adult and developing human cerebella exhibit different profiles of opioid binding sites. *Brain Res*. 1990;523:62-8. https://doi.org/10.1016/0006-8993(90)91635-t

SUPPLEMENTAL FILES

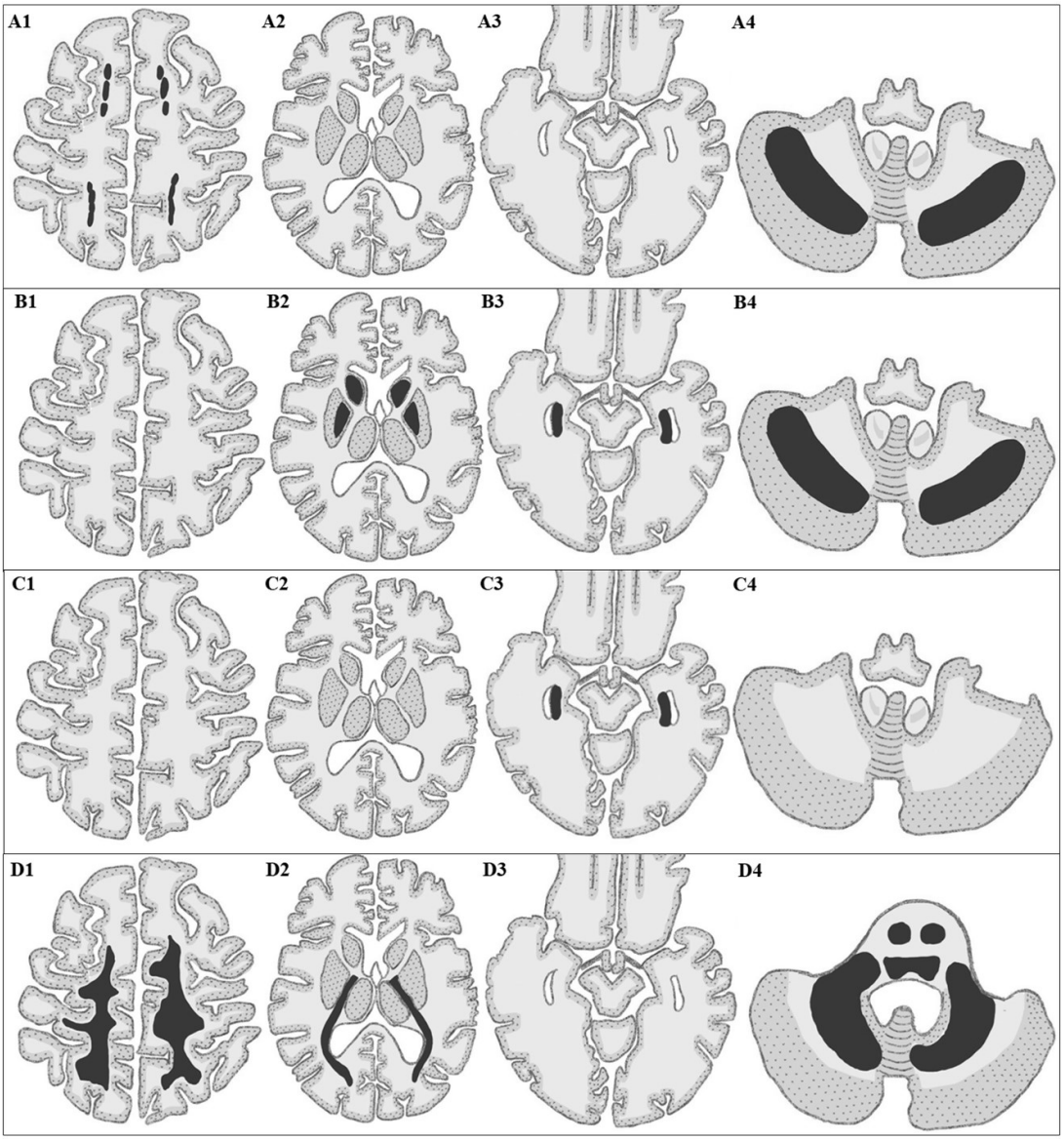
Online Supplemental Data 1: Table summarizing clinical and imaging features, treatment and follow up of patients in the clinical report

Patient	Age (in years)/ Sex	Clinical presentation	Blood Investigations	Imaging features	Treatment	Follow up
1	4/F	**Symptoms**- Sudden unresponsiveness 3 hours following ingestion of cough syrup containing dextromethorphan hydrobromide for low-grade fever, cough, and coryza. **Signs and examination -** Unconscious, bilateral pinpoint pupils, Body temperature: 102 °F (febrile), Heartbeat: 188 beats/minute (tachycardia), Blood pressure: 131/ 67 mmHg (systolic/ diastolic: elevated), SpO_2: 75% (low), Needle-stick blood glucose level: 43 mg/dl (hypoglycemia), Generalized hypotonia with brisk deep tendon reflexes, and bilateral extensor plantar	• Cell counts: normal • Serum transaminases: AST – 56 IU/L, ALT – 197 IU/L (elevated) • Smear for malarial parasites: negative • Serum IgM ELISA for Dengue and scrub typhus: negative • Serum IgG antibodies for COVID-19: positive • CSF examination: normal	• Symmetrical and confluent diffusion restricting areas with corresponding T2/FLAIR hyperintensities in bilateral cerebellar hemispheres • Near symmetrical linear diffusion restricting foci with corresponding T2/FLAIR hyperintensities in bilateral centrum semiovale	• Emergent measures: securing the airway with intubation, administering 10% dextrose bolus for hypoglycemia • Bolus doses of Naloxone followed by an infusion for 48 hours along with measures to reduce intracranial pressure • Methyl prednisolone pulse therapy for five days, followed by oral prednisolone for two weeks	Normal neurological examination
2	2/M	**Symptoms-** Unresponsiveness after 1 hour of ingestion of cough syrup containing dextromethorphan hydrobromide for fever and upper respiratory tract illness. Seven brief episodes of generalized tonic-clonic seizures on the way to our hospital.	• Cell counts: normal • Serum transaminases: AST – 118 IU/L, ALT – 41 IU/L (elevated) • Smear for malarial parasites: negative • Serum IgM ELISA for Dengue, and	• Near Symmetrical and confluent diffusion restricting areas with corresponding T2/FLAIR hyperintensities in bilateral cerebellar hemispheres • Symmetrical linear diffusion restricting foci in bilateral centrum		Normal neurological examination

		Signs and examination - Unconscious, bilateral pinpoint pupils, Body temperature: 100º F (febrile), Heartbeat: 148 beats/min (tachycardia), Blood pressure: 102/53 mm Hg (systolic/ diastolic), Needle-stick blood glucose of 92 mg/dl, Generalized hypotonia with brisk deep tendon reflexes and bilateral extensor plantar	scrub typhus: negative • Antibodies for COVID-19: negative • CSF examination: normal	semiovale and deep white matter • Few diffusion restricting foci in left caudate nucleus and bilateral posterior putamina	
3	1.5/F	**Symptoms:** Decreased responsiveness for 2 hours after ingestion of cough syrup containing dextromethorphan hydrobromide with intermittent fever and dry cough. Single seizure episode. **Signs and examination**: Lethargic, bilateral constricted pupils Body temperature: 100º F (febrile), Heartbeat:134 beats/min, Blood Pressure:110/80 mm Hg (systolic/diastolic), SpO_2 of 54% (respiratory failure), Needle-stick blood glucose level: 42 mg/dl (hypoglycemia)	• Serum transaminases: AST – 128.9 IU/L, ALT – 43.9 IU/L (elevated) • Smear for malarial parasites: negative • Serum IgM ELISA for Dengue, and scrub typhus: negative • Antibodies for COVID-19: negative • CKMB: 61.4 (raised) • CKNAC: (1095) raised • Hyperkalemia • IL-6: 133 pg/ml (high) • CSF examination: normal	• Symmetrical and confluent diffusion restricting areas with corresponding T2/FLAIR hyperintensities in bilateral cerebellar hemispheres	Normal neurological examination. MR done 2 weeks later: significant resolution of T2/FLAIR hyperintensities in cerebellum with normalization of restricted diffusion

AST: Aspartate Transaminase, ALT: Alanine Transaminase, ELISA: Enzyme Linked Immunosorbent Assay, CKMB: Creatine Kinase MB

Online Supplemental Data 2:



Supplemental Image 1: Illustration showing typical brain involvement in various opioid overdose/ toxicity syndromes. Axial brain images (self-drawn) representing MR brain sections at high supratentorial white matter level (A1, B1, C1, D1), at basal ganglia level (A2, B2, C2, D2), at hippocampus level (A3, B3, C3, D3) and at brainstem and cerebellum level (A4, B4, C4, D4) showing edema (on diffusion weighted sequence or T2W sequence) in black color. **A: Illustration of POUNCE (pediatric opioid use-associated neurotoxicity with cerebellar edema) syndrome** (prevalent in children) showing linear diffusion restricting or T2W hyperintense foci in supratentorial white matter (A1), no involvement of basal ganglia (A2) or hippocampi (A3) and confluent symmetric edema in bilateral cerebellar hemispheres (A4). DANCE (Dextromethorphan Associated Neurotoxicity with Cerebellar Edema) syndrome described in our case series shows a striking resemblance to POUNCE syndrome. **B: Illustration of CHANTER** (Cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion) syndrome (prevalent in adults) showing no involvement of supratentorial white matter (B1). Edema (T2W hyperintensity with restricted diffusion) is seen in bilateral basal ganglia (B2), bilateral hippocampi (B3) and in bilateral cerebellar hemispheres (B4). **C. Illustration of OAA (Opioid Associated Amnestic) syndrome** (prevalent in adults, mild prognosis as compared to other opioid syndromes) showing edema (T2W hyperintensity with restricted diffusion) in bilateral hippocampi (C3) with no involvement of supratentorial white matter (C1), basal ganglia (C2) or cerebellar hemispheres (C4). **D. Illustration of "chasing the dragon" leukoencephalopathy following chronic inhalation of heroin vapors (other 3 opioid syndromes are following acute opioid ingestion).** D1: Confluent T2W/ FLAIR hyperintensities are seen in supratentorial deep white matter, with preference for posterior white matter and sparing of

subcortical U fibres. D2: Symmetric T2W hyperintensities are seen in posterior limbs of bilateral internal capsules and bilateral optic radiations. D3: Hippocampus is not involved. D4: Confluent and symmetric white matter T2 hyperintensities are seen in a butterfly wing pattern involving bilateral middle cerebellar peduncles and contiguously cerebellar white matter with sparing of dentate nuclei and cerebellar cortex. Abnormal T2 hyperintensities are also seen in pons involving the corticospinal tracts (two black structures drawn on ventral aspect of pons) and medial lemnisci and central tegmental tracts (structures drawn on dorsal aspect of pons).