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CASE REPORT

Case Report: Morphine withdrawal induced convulsions in an adult male patient [version 1; peer review: 2 approved with reservations]

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Abstract

This case report describes a possible unknown complication of morphine withdrawal in a patient with persistent back pain, treated with intrathecal morphine pump infusion. The patient presented with left lower extremity edema. After excluding deep vein thrombosis by Doppler ultrasound and worsening of the swelling despite oral antibiotics, peripheral edema caused by intrathecal morphine was suspected. Twelve hours following the termination of his intrathecal morphine pump and initiation of inequivalent doses of oral morphine and tramadol, he developed convulsions. After metabolic and structural causes of convulsion were ruled out by blood tests and head imaging, equivalent doses of morphine were given. Then the patient regained full consciousness, and no additional seizures occurred. After that, opioid withdrawal emerged as the most likely explanation. Seizure is a life-threatening condition; therefore, an awareness of this case is important and further studies are warranted to explore the potential association of opioid withdrawal and seizure.

Keywords

Morphine, Seizure, Withdrawal, Intrathecal morphine, Opioid, Convulsion

Open Peer Review

Approval Status

	1	2
version 1
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1. Johnson Pradeep Ruben , St. John's Medical College and Hospital, Karnataka, India		
2. Carlos Arias Morales , City University of New York (CUNY), New York City, USA Albert Einstein College of Medicine, New York City, USA		

Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Morphine withdrawal is a common medical problem. Patients with morphine withdrawal can present with a variety of symptoms including runny nose, watery eyes, fever, vomiting, nausea, headaches, sweating, chills, muscle aches, diarrhea, high blood pressure, agitation, anxiety, irritability, depression, disorientation, insomnia¹. This case report describes a seizure as a clinical complication during an adult male patient's withdrawal from morphine. The link between opioid withdrawal and seizures is not well studied in adult humans. To the best of our knowledge, only two case series of seven patients and three patients have been reported tying opioid withdrawal to seizures^{2,3}.

Case presentation

A 44-year-old Qatari man known to have persistent back pain admitted to our facility in 2017. He presented with left lower extremity edema that started approximately three to four weeks prior to admission. It was affecting his daily activities like showering and driving. The edema began in his foot and then gradually progressed to his abdomen. A physical examination found soft pitting edema in the left lower limb up to the sacrum posteriorly and to the umbilicus anteriorly. His lower limb showed some redness with no hotness, tenderness, or signs of chronic venous insufficiency. His past surgical history demonstrated multiple back surgeries, as follows; in 1986, he underwent surgical correction and fusion of lumbar scoliosis anteriorly and posteriorly. Additionally, in 1986, he had triple arthrodesis of his right foot. In 1992, he underwent lengthening of his atrophic flail right leg. In 1993, the Harrington rod from the dorsal and lumbar spine was removed. In 2004, he had anterior lumbar interbody fusion with cages at the levels of T10-T11 and T11-T12. In 2008, he underwent revision surgery to extend the anterior instrumentation from T2 to T12. In March of 2014, the patient had intrathecal morphine pump inserted with a morphine infusion rate of 5.75 mg/day.

Upon admission, a Doppler ultrasound scan of his left lower limb revealed no evidence of deep vein thrombosis (Figure 1). The patient was started empirically on amoxicillin-clavulanic acid (875 mg orally every 12 hours for five days), suspecting community-acquired cellulitis as one of the common causes of unilateral lower limb edema, but his edema did not improve. On the fifth day of admission, the patient started to develop new edema on the right leg. A pelvic and abdominal ultrasound scan showed no obvious mass (Figure 2). We then suspected that his intrathecal morphine infusion may be the cause of his peripheral edema, as other common causes were excluded, so the morphine pump was halted, and the pain management team initiated the patient on oral morphine (30 mg) twice daily and tramadol (50 mg) every six hours.

After twelve hours from pump termination, the patient started to convulse. He had three episodes of convulsion over two hours in

the form of generalized tonic-clonic convulsion with rolled-up eyes; each episode was preceded by progressive muscle twitches. They were associated with continuous high blood pressure, ranging from 180/100 mmHg to 210/110 mmHg, and profuse sweating. All of the seizure episodes were aborted within a few seconds following the administration of 5mg intravenous diazepam, which was administered one to two minutes after the seizure started. Four hours later, another three seizure episodes occurred. The first was aborted by 5mg intravenous diazepam and the other two episodes required 10mg of intravenous diazepam.

A computed tomography review of the patient's head was grossly normal and revealed no acute intracranial event (Figure 3). A complete metabolic panel was done and revealed no acute metabolic process or hypoglycemia. The patient's morphine regimen changed to 5 mg administered intravenously every four hours with oral tramadol (50 mg) every six hours. In the evening, the patient regained full consciousness and no additional seizures occurred.

Upon patient request, the intrathecal morphine pump was restarted. One day after, the patient's swelling in left lower limb started to increase so the intrathecal morphine pump was stopped, and the patient was started on patient-controlled analgesia fentanyl (50 mcg/hour) and oral methadone (10 mg every six hours). His left- and right-side edema disappeared gradually over seven days and after he regained his baseline functional capacity, he was discharged.

Discussion

Central nervous system irritability is a known opioid withdrawal sign in neonates⁴ and is accompanied by seizures in 2% to 11% of cases^{5,6}. While a high degree of cerebral activity and seizure has been reported in rodent model opioid withdrawal studies⁷, the link between opioid withdrawal and seizures is not well studied in adult humans. To the best of our knowledge, only two case series of seven patients and three patients have been reported tying opioid withdrawal to seizures^{2,3}.

Our patient was not known to be an opioid addict from their history and their opioid risk tool score of one⁸, so the concurrent use of another known seizure-inducing substance was unlikely. He was receiving an intrathecal dose of morphine which changed to an unequal oral dose of morphine, in addition to tramadol. Seizures are not mentioned in the literature as a known complication of morphine withdrawal, and the patient's complication may have been caused by severe pain accompanied by inadequate doses of analgesics.

Conclusions

This case illustrates a possible connection between opioid withdrawal and seizure in an adult male patient. Seizure is a

Figure 1. Doppler ultrasound scan for the left lower limb. **A** and **B**) left common femoral vein; **C**, **D** and **E**) left superficial femoral vein; **F**) left popliteal.

Figure 2. Ultrasound scan of abdomen. A) urinary bladder; **B)** urinary bladder postvoid; **C)** mid abdomen; **D)** gallbladder; **E)** right kidney; **F)** left kidney; **G)** spleen.

Figure 3. A–E) Computed tomography of the patient's head.

life-threatening condition; therefore, an awareness of this case is important and further studies are warranted to explore the potential association of opioid withdrawal and seizure.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Current Peer Review Status: ? ?

Version 1

Reviewer Report 13 July 2020

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? **Carlos Arias Morales**

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- Ali and collaborators describe a case of a possible association between opioid withdrawal and seizure-like activity. As stated by the authors, there are only a few cases reported in the literature that associate opioid use and this type of complication.
- The case history and progression has been described in detail. However, there are some points that need to be addressed. Surgical history could be summarized in a way that readers have the idea of an extensive orthopedic surgery history without providing specific details about those procedures, such as the year when they were performed.
- It is stated by the authors that the pain management team initiated the oral opioid treatment after the discontinuation of intrathecal pump. It would be helpful to know if the team made the switch based on opioid conversion tables to provide the patient with equianalgesic doses. Additionally, it will be helpful to know if a urine drug screen was performed upon admission to rule out illegal substance use that could potentially cause seizures.
- The discussion section needs to be extended. The authors state there is a lack of literature regarding the association between opioid withdrawal and seizure-like activity. However, there have been some articles proposing a potential mechanism for which seizures may occur in those cases (Khanra *et al.*, 2015¹).
- Also, the authors stated that in their case the seizure may have been caused by severe pain and inadequate doses of analgesics. However, when making conclusions they state that the case illustrates a possible connection between opioid withdrawal and seizure, which creates a contradiction. It is advised that the authors review the cited article on this report regarding potential mechanism of seizure-like activity in chronic opioid use. Lastly, the manuscript needs to be revised for grammar and semantics.

- Kindly revise the above observations.

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Internal medicine, clinical medicine research, neuroscience research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 09 September 2019

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Johnson Pradeep Ruben

Department of Psychiatry, St. John's Medical College and Hospital, Karnataka, India

The Case report is interesting and very useful. There are few suggestions.

1. There needs to be more details about the use of opioids in the past surgeries, whether the patient was dependent to Opioids in the past?

2. Did the patient have status epilepticus?
 3. More information about what blood investigations were done and details about the same.
 4. Discussion is very superficial and the pathophysiology of seizures in a opioid withdrawal needs to be discussed.
- Kindly answer the above questions.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Addiction Psychiatry, Child Psychiatry, Resilience in wives of alcoholism,

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Sep 2019

Mahmoud Ali, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar

Thank you for your informative review

1. The patient used the opioid "morphine and fentanyl" during the post-operative periods only. The doses during those times are not well accurate. Our patient was not known to be an opioid addict from their history and their opioid risk tool score of one
2. The patient did not have status epilepticus, as he was regaining his full conscious in between the attacks.
3. Blood investigations which sent were;
 - Complete blood count.
 - A complete metabolic panel which includes "renal function tests, Liver function tests, calcium, phosphorus, magnesium, and albumen."
 - Random blood sugar.
 - Sepsis workup which includes "blood cultures, CRP, and procalcitonin."

1. Seizures in an opioid withdrawal in adults are not well known, and there is no much data about its pathophysiology.

Competing Interests: I do not have any competing interests

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