CASE REPORT

DOI: 10.5336/caserep.2024-105224

Fatal Case of Opioid Overdose with Somatic Comorbidity: A Case Report and Review

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This study was presented as an poster presentation at 2nd International Case Report Congress, April 5-7, 2024, Skopje, Macedonia.

ABSTRACT Clinicians in the emergency department are often confronted with coma patients due to poisoning. Clinical neurological evaluation, technical investigations like computed tomography (CT)-scan and laboratory (including toxicological) tests should be part of a careful diagnostic plan. Opiate-addicted individuals have a higher risk of stroke than the general population. A comatose 47-year-old female patient with opioid use disorder was brought by ambulance to the University Clinic for Toxicology in Skopje. The family's suspicion was that perhaps the new condition was caused by excessive intake of alcohol or methadone or both. CT of the brain showed an ischemic stroke with a compressive effect on the left lateral chamber. After 11 days the condition of the patient deteriorated and resulted in death. The aim of this report was to emphasize the diagnostic challenges that clinicians encounter when dealing with a comatose patient and clinical importance of differentiating between opioid overdose and other somatic comorbidities.

Keywords: Opioid-related disorders; opiate overdose; stroke; hemiplegia

Clinicians in the emergency department are often confronted with coma patients due to poisoning.[1] A comatose state in a patient could be caused by either non-toxicological trigger (e.g., "neurological, infectious or metabolic disorders") or by numerous drugs and toxins.[2] Drug abusers have an increased risk of both hemorrhagic and ischemic stroke. The illicit drugs more commonly associated with stroke are psychomotor stimulants, such as amphetamine and cocaine. Less commonly implicated are opioids and psychotomimetic drugs, including cannabis. Toxicology screening for illicit drugs should be done in young patients with stroke with no obvious cause, or if suggested by history or examination.[3,4] We chose this case because we believe it will contribute to existing literature. The aim of this report was to emphasize the diagnostic challenges that clinicians encounter when dealing with a comatose patient and clinical importance of differentiating between opioid overdose and other somatic comorbidities.

CASE REPORT

A 47-year-old female patient, in a comatose state, was brought by ambulance to the University Clinic for Toxicology in Skopje. The patient has had opioid use disorder for more than 20 years; she has been on regular substitution therapy with 100 mg methadone (Alkaloid, Skopje, Republic of North Macedonia) for almost 7 years and in the last year with increased al-

TO CITE THIS ARTICLE:
Simonovska N, Babulovska A, Pereska Z, Naumovski K, Kostadinovski K. Fatal case of opioid overdose with somatic comorbidity: A case report and review. Turkiye Klinikleri J Case Rep. 2025;33(2):43-7.

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Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 22 Aug 2024 ***Accepted:*** 23 Dec 2024 ***Available online:*** 21 Mar 2025

cohol use. Her medical history included tuberculosis and chronic obstructive pulmonary disease, and she had been treated for thrombosis of the lower extremities but without clear information about the course of her treatment. She had a history of intravenous application of opioids as well.

The family had no precise information concerning the patient's new state. The last communication with the patient was made approximately 8-9 hours prior to admission. The family suspected that the condition occurred due to methadone and alcohol intake.

On admission, the patient was comatose, Glasgow Coma Scale-5 (eye response=2; verbal response=2; motor response=1), with miosis. Blood pressure was 90/60 mmHg, body temperature was 37 °C, with oxygen saturation on room air from 85 up to 92%, weakened vesicular breathing in the basal parts of the right lung, soft abdomen, and skin changes of the extremities. Electrocardiogram was with sinus rhythm hazard ratios=110/min, QRS complex=100 msec, corrected QT interval=400 msec, without other changes.

The protocol followed was ABCDE approach regarding a comatose patient. Treatment was immediately started with coma cocktail (dextrose, oxygen, naloxone, and thiamine), which did not improve the patient's condition.

The patient was anti hepatitis C virus positive and coronavirus disease-2019 rapid antigen test was negative. On admission, laboratory and toxicological analyses were performed. Laboratory findings showed increased levels of C-reactive protein, lactate dehydrogenase, troponin, creatine kinase, creatine kinase-myocardial band and decreased levels of platelets, sodium, potassium. Hemostasis tests were within reference range except for D-dimers (Table 1).

Toxicological analyses were performed on Beckman Coulter AU480 Analyzer-enzyme (Beckman Coulter, Inc., USA) immunoassay technique (Table 2).

Blood gas analyses were performed with oxygen support by face mask (PH: 7.54; pCO_2: 5.47 kPa; pO_2: 9.0 kPa; base excess: 13.5; $cHCO_3$: 35.6).

Next day the patient was still in a coma, without verbal response, with eye response to pain, mild abnormal extension of left arm and left leg, without motor response of right arm and right leg. An urgent brain computed tomography (CT) scan showed an ischemic stroke with a compressive effect on the left lateral chamber (Figure 1).

Since sodium and potassium on admission were below reference values (sodium: 124 mmol/l; potassium: 3 mmol/l) the treatment was continued with 10% sodium chloride and when normal sodium levels were obtained, it was continued with sodium chloride (0.9% NaCl) at a dose regime of 2.5 mL/kg/h intravenous (iv) infusion, 7.46% potassium chloride 10 mmol/hr by monitoring the potassium level, low molecular heparin therapy [enoxaparin (Sanofi Winthrop Industrie, France) 1 mg/kg] and ceftriaxone (Turkish pharmaceutical compan) 2 gr/day. The treatment was based on early and intensive fluid therapy, oxygen support by face mask 2-4 L/min.

TABLE 1: Laboratory analysis

	Result	Reference value	Unit
Platelets	95	140-450	10^9/l
D-dimers	3921	<500	ng/ml
CRP	32.5	<6	mg/L
LDH	478.0	<248	U/L
Troponin I	635.8	<15.6	ng/L
CK	317.0	24-173	U/L
CK-MB	65.4	<25	U/L
Sodium	124.0	137-145	mmol/L
Potassium	3.0	3.8-5.5	mmol/L

CRP: C-reactive protein; LDH: Lactate dehydrogenase; CK: Creatine kinase; CK/MB: Creatine kinase-myocardial band

TABLE 2: Toxicology screen

	Result	Reference value	Units
s-Alcohol	67.0	<100; <1‰-low intoxication	mg/dL
u-THC	25.0	<25-negative	ng/mL
u-Cocaine	58.0	<300-negative	ng/mL
u-Opiates	30.0	<300-negative	ng/mL
u-Amphetamine	220.0	<1000-negative	ng/mL
u-Methadone	**1135.0**	**<300-negative**	ng/mL
u-Benzodiazepines	14.0	<200-negative	ng/mL
u-Ecstasy	48.0	<1000-negative	ng/mL
u-Tramadol	15.0	<200-negative	ng/mL
u-Buprenorphine	5.0	<10-negative	ng/mL

THC: Tetrahydrocannabinol; s: Serum; u: Urine

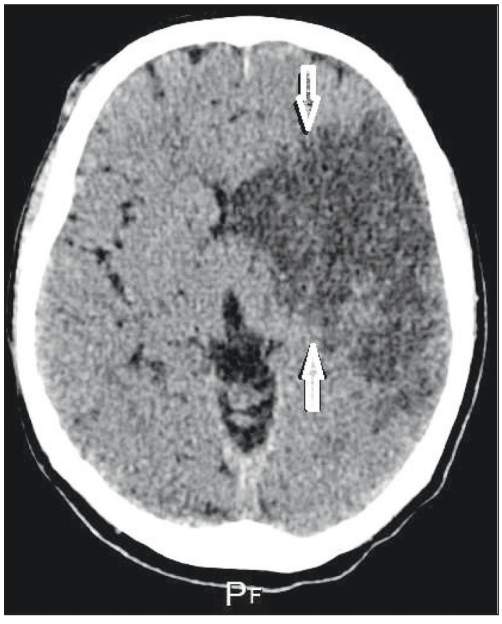

FIGURE 1: CT of brain Temporoparietal ischemic stroke with a compressive effect on the left lateral chamber

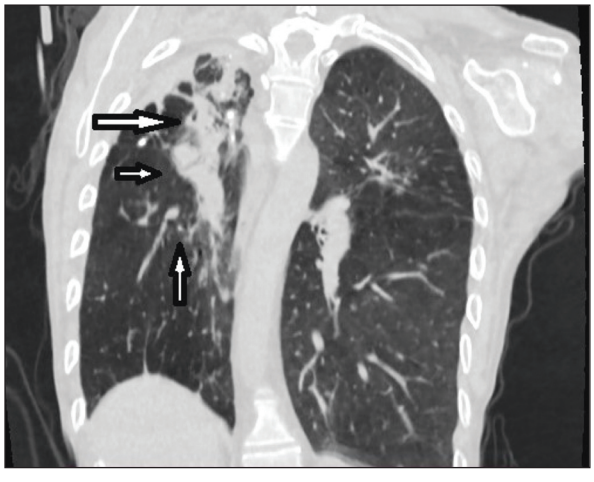

FIGURE 2: CT of the chest Homogeneous opacification in the right upper lobe from probably pleural encapsulation, gross fibro indurative changes hyloapically with intrafocal mesthymic small calcifications on the right, at that level with elevation of the hilus. Trachea and mediastinum drawn to the right, as well as the cardiac silhouette

Due to the concomitant comorbidities, other investigations like chest X-ray and CT of the lungs were performed (Figure 2).

Sputum tests [GeneXpert (Cepheid, USA), Löwenstein-Jensen culture, Fluorescence Microscopy] for an active tuberculosis process were negative.

The ultrasound of the abdomen was with normal findings and color dopler echocardiography was without any registered disturbances in the segmental kinetics of the left ventricle. Valvular apparatus was morphologically and functionally adjusted for age and pericardium was normal.

A consultation with a pulmonologist and a neurologist was made.

Despite all investigations and continuous treatment, 11 days after hospitalization, the patient developed cardiorespiratory failure and died.

Informed consent has been obtained from the patient's relatives.

DISCUSSION

Opiate-addicted individuals have a higher risk of stroke than the general population. Pulmonary embolism and stroke occur because of deep venous thrombosis after intravenous use of illicit drugs.[4-6] In one study out of total 595 cases with first-ever stroke, 82 participants were with substance use disorder, of which 76.8% were with ischemic stroke.[7] Another study conducted between 1993 and 2015, the authors identified 5,283 patients hospitalized with stroke associated with infective endocarditis and opioid use (mean age of 41.2 years). Ischemic stroke accounted for 71.5% of hospitalizations and hemorrhagic stroke accounted for 28.5%. The greatest increases occurred in women and those <45 years old over the past decade.[8]

We have presented the case of a 47-year-old female patient in a comatose state with differential diagnostic difficulties. She has had opioid use disorder for more than 20 years and has been on regular methadone substitution therapy for almost 7 years. The neurological examinations and brain CT scan showed an ischemic stroke with a compressive effect on the left lateral chamber.

The opioid epidemic has led to the creation of a new term Toxic Brain Injury because of prolonged substance misuse and nonfatal overdose. This encompasses two forms of brain injury resulting from a lack of oxygen-hypoxic and anoxic brain injury. The amount of time the brain is without adequate oxygen dictates the severity of injury. It is essential to provide parallel treatment for both brain injury and substance misuse disorders. Oftentimes, substance

misuse is overlooked in the treatment of brain injury because the symptoms of intoxication and brain injury can appear to be similar.[9]

The delayed onset of stroke after injection and the common occurrence of stroke after an unusually long period of abstinence suggest immune-mediated factors. Immune phenomena could apply to all drugs whether ingested or introduced parenterally.[10] Individuals who abuse illicit/controlled substances infected with hepatitis C and those who use alcohol chronically may have relative coagulopathies related to underlying liver disease and/or platelet abnormalities.[11]

Our patient, despite a history of intravenous application of opioids, was positive for hepatitis C and she had increased alcohol use in the last year as well. Her medical history included thrombosis of the lower extremities but without clear information about the course of her treatment. The use of methadone, history of intravenous application of opioids and thrombosis of lower extremities, the late diagnosis of ischemic stroke with a compressive effect on the left lateral chamber and the limitation regarding the inclusion of therapy according to the guidelines for the treatment of stroke, constant decrease of saturation with oxygen, the lack of oxygen in the brain, resulting with cardiorespiratory failure and fatal outcome in our patient.

In conclusion, it should be kept in mind that collecting patient's history, recognition of clinical symptoms and signs, appropriate investigations in comatose patients are essential to differentiate and identify the correct diagnosis.

The notable opioid prevalence mandates that physicians maintain a high index of suspicion when dealing with a comatose patient, especially if the patient has any known history of opioid use disorder. Healthcare professionals should be aware that a comatose state in a patient could be caused by either non-toxicological trigger or by toxic causes.

Acknowledgements

The authors are grateful to the University Clinic for Toxicology for facilitating this work and Lenche Danevska for English proofreading of the manuscript.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Natasha Simonovska;* ***Design:*** *Natasha Simonovska, Zanina Pereska;* ***Control/Supervision:*** *Natasha Simonovska;* ***Data Collection and/or Processing:*** *Kiril Naumovski, Kristin Kostadinovski;* ***Analysis and/or Interpretation:*** *Aleksandra Babulovska;* ***Literature Review:*** *Natasha Simonovska, Zanina Pereska;* ***Writing the Article:*** *Kiril Naumovski, Kristin Kostadinovski;* ***Critical Review:*** *Aleksandra Babulovska;* ***References and Fundings:*** *Natasha Simonovska;* ***Materials:*** *Kristin Kostadinovski.*

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