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Toxicology

Lead poisoning due to ingestion of lead-contaminated opium: A diagnostic study on patients' imaging findings

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ABSTRACT

Objectives: Our study attempts to determine if for patients following ingestion of lead-contaminated opium, radiographs [plain X-ray (KUB)] or unenhanced computed tomography (CT scan) of the abdomen may be predictive of lead poisoning.

Methods: Our study is concerned with patients of > 21 years with elevated lead concentrations, who had undergone KUB or CT. Patients with other toxicities who had undergone similar imaging profiles but who had low blood lead level (BLL) were enrolled as controls.

Results: We evaluated a total of 79 cases and 79 controls with median [IQR] BLLs of 126 [97.4, 160] μg/dL and 8.7 [5.5, 15] μg/dL. All cases and eleven controls (13.9%) were addicted to oral opium, and of these cases, anemia (94.9%) and abdominal pain (92.4%) were the two most common clinical manifestations. Two radiologists reviewed the X-ray and non-contrast CTs. Fifty (63.3%) and 53 (67.1%) cases and controls underwent CT scanning with 34 (68%) vs. 6 (11.3%) positive CTs ($P < 0.001$) while 43 (54.4%) and 39 (43.3%) underwent X-rays with 21 (48.8%) vs. 4 (11.8%) positive X-rays, respectively ($P < 0.001$). Positive CT is associated with BLL between 10 and 45 μg/dL with a specificity of 96.9%, 88.7% and positive predictive value of 97.5% and 85% respectively.

Conclusions: In suspected cases of lead exposure due to ingested opium, and if BLL is not readily available, a positive imaging result may guide radiologists and physicians to consider lead poisoning.

1. Introduction

Lead is an environmental hazard with potential adverse health effects, such as affecting the central nervous system as well as hematopoietic, hepatic, and renal systems causing serious medical ailments, including death [1,2]. Clinically significant acute lead toxicity is less common than chronic toxicity. Persistent vomiting, encephalopathy, lethargy, delirium, convulsions, and coma all characterize severe lead poisoning [3,4].

The United States Centers for Disease Control and Prevention (CDC) has set a BLL guideline at 10 μg/dL and 5 μg/dL in the adults' and children's whole blood, respectively [5]. Clinical manifestations may change depending on other environmental factors [6].

Common in several media including water, soil, air, and food, lead enters the body through inhalation, ingestion, or less commonly dermal contact [7,8]. In adults, lead toxicity may occur in substance abusers [9,10]. In Iran, where opium abuse is extremely high [11], lead-contaminated opium, as recently as 2016, has caused an outbreak of lead poisoning with almost 4000 lead-poisoned patients referring to hospital [12]. Lead may be added to opium to increase its weight as an adulterant. This is referred to as "stepping or blow up", where the purity is decreased but the weight is increased to increase profits [13–16]. In Iran, opium is adulterated also with soil, minced liver, flour, burned oil, tea, cacao, Indian henna, decoction of jute leaves, artificial leather, dried animal blood, melted X-ray films and pharmaceutical opioids, particularly tramadol [17,18].

Because few Iranian laboratories are equipped with atomic absorption technique to determine BLL, many patients are referred, without a BLL, to hospitals with abdominal colic. Hospitals without readily available blood lead analytical equipment, which may delay the

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diagnosis and treatment. In order to expedite a diagnosis of lead contamination in patients, we studied imaging as a possible determinant for the presence of lead.

2. Material and methods

Patients admitted to Loghman-Hakim Hospital Poison Center (LHHPC) in Tehran, Iran during an outbreak from March 2016 to December 2017 voluntarily participated in the study. From each voluntary patient, we collected standardized data.

Using the data collection sheet that we developed prior to patient enrollment, treating toxicologists gathered information. Consecutively enrolled were hospitalized patients with BLL and confirmed diagnosis of lead exposure (BLLs > 45 μg/dL as well as clinical manifestations of lead poisoning including anemia, abdominal pain, paresthesia, seizure, constipation, and etc. in patients 21 years of age or older who had undergone KUB and/or CT scan. Imaging studies had been performed to work-up abdominal symptoms and exclude drug smuggling.

The control group comprised patients who had been admitted to toxicology ward due to toxicities other than lead poisoning (had no signs or symptoms of lead toxicity) and who, before or during hospitalization, had undergone KUB and/or CT scan. These patients were intoxicated with specific poisons, including zinc phosphide, iron and gastrointestinal concealment of drugs, that mandated abdominal imaging (Fig. 1) [16,19–21]. Blood lead was assayed by atomic absorption spectroscopy (Graphite Tube Atomizer; GTA AAA 120; USA). Twenty-five microliters of the blood samples were taken by a sampler and poured into the test tubes. Then, 10 milliliters of matrix (0.25 ammonium dihydrogen phosphate + 0.2% nitric acid + 0.01% triton X100) as well as nitric acid 69% were added to the tube and mixed slowly. Finally, the solution was centrifuged (10,000 per minute). Standards were read and the calibration curve was drawn. If a control patient had a blood lead level greater than 45 ug/dL, they were considered to have lead exposure and excluded from the analysis.

There were no previous reports describing the lead particles in abdominal CT scan; thus, the threshold of 200 HU was assumptive according to the approximate density of foreign bodies in abdomen. Although we found no reference confirming this, we assumed at least three particles to be present to exclude other random contaminations.

Our data collection sheet asked for patients' gender and age, signs and symptoms of toxicity, time elapsed between initiation of signs and symptoms (latency) and hospital presentation, laboratory tests on presentation, type of the substance and duration of addiction, daily amount of substance abuse, amount of substituted methadone during hospitalization, BLL, treatment performed, and the findings of the imaging modality.

Ingested daily dose of the substances was estimated based on the ingested weight of the purchased drug (gram). Opiate-dependent patients were provided methadone during hospitalization [22]. To reduce potential sources of bias, we re-interviewed the patients before hospital discharge.

Technicians obtained plain radiographs (Bucky Röntgen DR Plus, X-Alliance, Germany) and/or abdominopelvic CT without oral or IV contrast using a 16 multi-detector CT scanner (Activion 16, Toshiba, Japan) and using the following parameters: Tube potential: 120 kV, Tube charge: automated mA, Pitch Factor: 1.4, rotation time: 0.75 s, Section thickness and interval: 5 mm and 2.5 mm, respectively. Images were stored in PACS (Picture Achieving and Communication System), (Medal Electronic Workstation, Tehran, Iran), and afterwards a board-certified radiologist with five years of experience in abdominal imaging and his senior resident reviewed the unblinded images. The cases and controls were mixed randomly and both interpreters were blinded to the clinical results. In cases when patient had both radiograph and CT scan, the scans were viewed separately. All the images were reviewed using a dedicated diagnostic monitor. If there were any conflicting results, the file was re-reviewed by both radiologists and an inter-observer agreement was made. Two attending physicians completed the standardized data forms.

Based on the radiopaque particles detected, imaging studies (KUB and/or CT scans) were reported to be positive or negative. When particles within the gastrointestinal tract with visual opacity similar or denser compared to adjacent bony structures (Fig. 2) were present, KUBs were assumed positive. When three or more punctuate particles with the density of at least 200 Hounsfield units were detected in gastrointestinal tract, CT scans were determined to be positive (Fig. 3). Because of the small size of the foci, a pixel densitometer was used instead of measurement by region of interest (ROI).

We performed a subsequent analysis between patients with abnormal BLL (> 10 μg/dL) and normal BLL (≤ 10 μg/dL). Abdominal X-ray and CT findings were pooled to create "imaging" or "total" cases and considered to be positive if either X-ray or CT scan was positive. Otherwise, imaging findings were documented to be negative. Regarding patients who underwent both techniques to determine the difference, if any, between abdominal X-ray and CT scan, we performed a sub analysis.

For the control group, our Institutional Review Board (IRB) waived informed consent for non-interventional studies. For case patients, the IRB granted approval. Before undergoing diagnostic interventions, patients submitted a written consent. Regarding patients who had referred with loss of consciousness and with possible diagnosis of lead encephalopathy, informed consent was waived due to the emergent nature of toxicity.

Considering an average positive X-ray of 26% in ingested lead exposure [23], the desired 95% level of confidence, and the desired ±

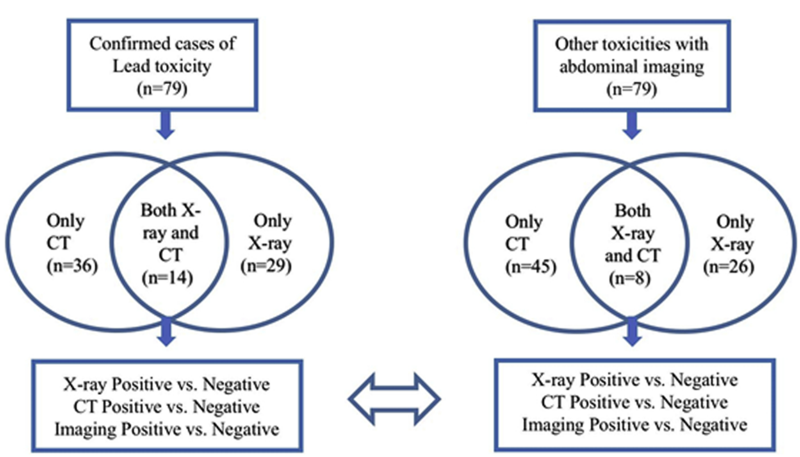

Fig. 1. Protocol of patients' recruitment in the study.

Fig. 2. Plain abdominal X-ray shows innumerable tiny dense opacities dispersed within the cecum, ascending and sigmoid colon.

10% accepted margin of error, a sample size of 74 was determined to study the diagnostic efficacy of abdominal X-ray and/or abdomino-pelvic CT scan in determining lead exposure. Seventy-nine subjects were recruited in case and control groups for analysis.

For the description of quantitative variables with normal and non-normal distribution, we used mean (± SD) and median (interquartile rage), respectively. For qualitative variables, we noted percent of frequency. To compare continuous variables between the two groups, if variables were normally distributed, we applied *t*-test and for abnormally distributed, we applied the Mann-Whitney U test. To evaluate the association between categorical variables, we employed chi-square or Fisher's Exact test. Moreover, we used odds ratio (OR) and 95% confidence interval (CI) to express the power of this association. We performed multivariable analysis by constructing a logistic regression model. Additionally, for multivariable analysis, we tested all variables showing significant correlation with lead exposure (case group) and imaging studies (CT scan/X-ray/Both pooled techniques) in univariate analysis. In a regression model, we entered all variables with P value less than 0.05 in their univariate analysis to determine independent variables that predicted positive/negative CT scan/X-ray and lead exposure using forward Wald method. By generating receiver operating characteristic (ROC) curve we tested the ability of imaging studies in predicting BLL. A P value less than 0.05 was considered to be statistically significant. For analysis, we used statistical package for social sciences (SPSS) version 17.0 (SPSS Inc., Chicago, Ill, USA).

3. Results

A total of 79 cases and an equal number of controls were studied. All cases were male oral opium consumers (versus 11 in control group; $P < 0.001$). Nausea and vomiting were more prevalent in controls cases 11 (13.9%), controls 28 (34.5%) (0.29 0.13 − 0.65). Shown in Table S1 are other signs and symptoms (abdominal pain, paresthesia, constipation, bone and muscle pain, and anemia). The median [IQR] (range) for BLL was 126 [97.4, 160] (47.3, 1124) μg/dL in cases and 8.7 [5.5, 15] (1.2, 39) μg/dL in controls ($P < 0.001$). The median age was higher in cases while median hemoglobin, hematocrit, and blood urea nitrogen were significantly lower than in controls (Table S2).

In cases patients, 50 (63.3%) underwent CT scan with 34 (68%) positive result and 43 (54.4%) underwent KUB with 21 (48.8%) positive study. Fourteen had both imaging modalities (Fig. 1). The reason for imaging studies was based on clinical signs and symptoms (especially abdominal pain) before confirming lead toxicity. All cases were addicted to oral opium, and body packing was included in the differential diagnosis inferring a need for CT. In this case, body packing in 21 (26.6%), zinc phosphide ingestion (a rodenticide) in 19 (23.8%), methamphetamine toxicity in 13 (16.5%), body stuffing in 9 (11.3%), opioids in eight (10.1%), pharmaceutical poisoning in five (6.3%), other intoxicants in three (3.8%), and corrosive ingestion in one (1.3%) patient. In the control group, 79 non-lead poisoned patients were recruited, of whom, 53 (67.1%) underwent CT scan with 6 (11.3%) positive study and 34 (43.4%) underwent plain X-ray with 4 (11.8%) positive result. Eight patients had both imaging modalities available in their files (Fig. 1).

A subgroup analysis of 22 patients with both imaging studies revealed that there was a significant difference between abdominal X-ray and CT scan in detection of lead-poisoned patients ($P = 0.001$). Cases were treated based on availability of chelating agents, BLLs, and clinical manifestations. D-penicillamine (36, 45.6%), BAL and EDTA (30, 38%), EDTA and D-penicillamine (7, 8.9%), EDTA (1, 1.3%), and BAL (1, 1.3%) were the treatments given to these patients. Three patients (3.8%) receive no antidote. Two lead-intoxicated patients died during

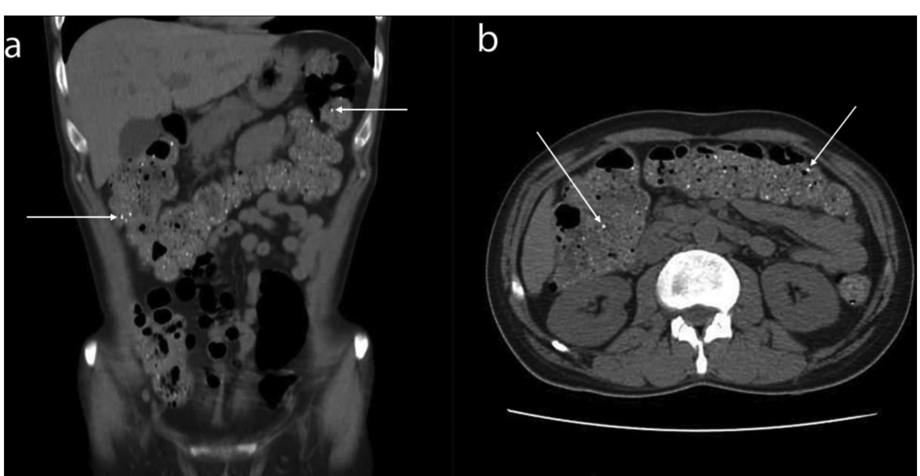

Fig. 3. Non-enhanced abdominal CT scan in axial(a) and coronal(b) views depict multiple small hyperdense foci with a punctuate appearance intermixed with fecal material in transverse colon, few of them marked by arrows.

Table 1
Quantitative variables of imaging studies in cases and controls.

	Case (n = 79)			Control (n = 79)			Total (n = 158)	
	+ Image (n = 48)	− Image (n = 31)	Sig.	+ Image (n = 10)	− Image (n = 69)	Sig.		Sig
Age (year)	47.7 ± 13.6 (26, 79)	49.7 ± 13.2 (30, 81)	0.577	33 [21, 44] (20, 74)	32 [24, 42] (14, 67)	0.774	41 [30, 53] (14, 81]	0.013
Duration of addiction (year)	15 [8, 20] (2, 50)	6.5 [3, 18.8] (1, 40)	0.017	–	–	–	12 [5,20] (1, 50)	–
Initiation of symptoms (hour)	20 [7, 30] (0, 90)	22 [5.2, 40.5] (0, 60)	0.789	5.5 [1.9, 39] (1, 48)	3 [2,18] (0.5, 61)	0.391	7 [3,24] (0, 90)	0.014
Opium daily dose (gram)	4 [3, 6] (1, 15)	2.8 [1.1, 3] (1, 5)	0.002	–	–	–	3 [2,5] (1, 15)	–
Blood Lead Level (µgr/dL)	124.5 [97.9, 160.7] (47.3, 248)	128 [95, 160] (50.4, 1124)	0.775	14.3 [9.8, 17.5] (1.2, 21)	8 [4.6, 14.2] (1.3, 39)	0.047	43.15 [8.71, 126.5] (1.2, 1124)	> 0.001
Hemoglobin (mg/dL)	9.5 ± 1.9 (5.7, 13.4)	9.5 ± 1.8 (6.5, 13.3)	0.790	14.6 ± 2.2 (10.4, 17.8)	14.8 ± 1.9 (10.8, 21.2)	0.852	14.0 [9.3, 14.5] (5.7, 21.2)	> 0.001
Hematocrit (%)	28.1 [25, 32.4] (19.2, 32.2)	29.4 [25.3, 32.5] (21.5, 39.2)	0.548	41.6 ± 5.4 (30.1, 47.7)	42.7 ± 4.6 (32.6, 53.2)	0.522	36.5 [28.2, 42.4] (19.2, 53.2)	> 0.001
Sodium (mEq/L)	142 [138, 143] (125, 146)	141 [139, 144] (132, 146)	0.894	139.5 [137.2,144.5] (133, 148)	141 [138.5, 144] (131, 149)	0.440	141 [138, 144] (125, 149)	0.621
Potassium (mEq/L)	4.2 [4, 4.4] (3.6, 5.2)	4.1[3.8, 4.7] (3, 5.1)	0.404	4.1 [3.9, 4.7] (3.1, 4.8)	4.1 [4, 4.3] (3.2, 5.5)	0.699	4.2 [4, 4.4] (3, 5.5)	0.122
Blood Urea Nitrogen (mg/dL)	27.5 [20, 39] (8, 80)	23 [17, 31] (12, 67)	0.246	35 [24, 43.5] (19, 95)	31.5 [26, 38] (15, 79)	0.643	29 [21,39] (8, 95)	0.719
Creatinine (mg/dL)	1 [0.9, 1.2] (0.7, 3.3)	1 [0.9, 1.1] (0.7, 1.5)	0.943	1 [0.9, 1.1] (0.8, 1.2)	1 [1, 1.1] (0.7, 1.8)	0.453	1 [0.9,1.1] (0.7, 3.3)	0.533
AST (U/L)	50 [32.2, 77.7] (17, 172)	38 [23.5, 48.5] (18, 117)	0.072	31.5 [20, 62] (15, 211)	24 [19, 32] (13, 618)	0.134	32 [21.7, 49.2] (13, 618)	> 0.001
ALT (U/L)	38 [25, 73.2] (10, 204)	34.5 [19.5, 58.7] (11, 142)	0.178	40 [14.5, 83] (8, 102)	22 [16.5, 34.5] (10, 530)	0.319	31 [19, 52] (8, 530)	> 0.001
BIL-Total (mg/dL)	1.2 [0.9, 1.7] (0.4, 4.2)	1 [0.8, 1.9] (0.5, 3.7)	0.809	0.9 [0.8, 1.2] (0.4, 1.7)	0.8 [0.6, 1.1] (0.2, 3.4)	0.650	0.95 [0.7, 1.52] (0.2, 4.2)	0.008
BIL-Direct (mg/dL)	0.4 [0.3, 0.6] (0.1, 3.1)	0.3 [0.3, 0.5] (0.1, 1.7)	0.284	0.3 [0.2, 0.4] (0.1, 0.6)	0.2 [0.2, 0.3] (0.1, 1.1)	0.230	0.3 [0.2, 0.5] (0.1, 3.1)	> 0.001
CPK (U/L)	62 [37.5, 118] (16, 495)	51.5 [35, 63.2] (20, 278)	0.136	157 [88.2, 1233.7] (48, 8356)	146 [87, 286] (28, 1097)	0.358	89.5 [52.7, 172.7] (16, 8356)	0.036
LDH U/L()	521 [407, 678] (292, 1400)	477 [428, 637] (364, 1106)	0.873	548 [432, 750.7] (313, 953)	491 [401, 586] (109, 1431)	0.342	491 [416, 628] (109, 1431)	0.380
Substituted methadone (mg/day)	30 [30, 71.2] (0, 180)	30 [0, 60] (0, 150)	0.179	0 (0, 10)	0 (0, 20)	0.606	0 [0, 30] (0, 180)	> 0.001

Values in median [IQR] using MVU, Values in mean ± SD* using *t*-test.

hospital stay due to lead encephalopathy.

We found correlation between abdominal X-ray findings and abdominal pain (P = 0.012), oral opium addiction (P = 0.02), anemia (P = 0.044), constipation (P = 0.033), BLL > 10 µg/dL (P = 0.002), and BLL > 45 µg/dL (P = 0.001). Referring to Table 1, CT had a significant correlation with abdominal pain (P < 0.001), oral opium addiction (P < 0.001), anemia (P < 0.001), bone and muscle pain (P = 0.013), constipation (P < 0.001), BLL > 10 µg/dL (P < 0.001), and BLL > 45 µg/dL (P < 0.001).

Table 2 shows median BLL in patients who have undergone abdominopelvic CT, abdominal X-ray, and both techniques in cases and controls. Table 3 illustrates a comparison of diagnostic efficacy of imaging findings in two cut-offs of BLL > 45 and BLL > 10 µg/dL. In controls (BLL < 45 µg/dL), those patients with higher BLLs had more frequent imaging densities (BLL of 14.4 versus 8 µg/dL).

For all opium patients, regardless of user case or control status, Table 4 shows all imaging findings. No correlation was detected between X-ray (5 cases, 17.9%), CT (29 cases, 64.4%) or combined imaging findings (32 cases, 47.1%) and ingestion of other substances. Of the opium patients in the control group none had positive CT results.

Considering all variables with significant P values for CT scan, X-ray, and combined imaging findings, BLL > 45 µg/dL was the only significant independent variable that predicted abnormal imaging findings. Logistic regression failed to show any independent variable that predicted BLL > 45 µg/dL (Table 5).

We performed receiver operating characteristic (ROC) analysis to determine the best cut-off point with the highest simultaneous sensitivity and specificity. The areas under the curves were 0.715 (95% confidence interval 0.602 − 0.827, P = 0.002), 0.806 (95% confidence interval 0.719 − 0.893, P < 0.001), and 0.777 (95% confidence interval 0.704 − 0.850, P < 0.001) for X-ray, CT, and combined imaging studies, respectively. With a sensitivity of 80%, 85%, 83% and specificity of 63.5%, 74.6%, 70%, X-ray, CT, and combined imaging findings were positive at BLL cut-off point of 72.5, 43.2, and 53.5 µg/dL, respectively.

4. Discussion

Recently, hundreds of people were admitted to the emergency departments with a common medical history of oral opium dependency. These patients were diagnosed by determination of BLL and treated by the standard toxicology treatment protocols, although BLL determination occasionally wa s delayed due to the limited number of centers equipped with atomic absorption technique coupled with the high number of the patients. This delay in chelation therapy may be harmful especially for those at risk of lead encephalopathy. On the other hand, because many patients' chief compliant was abdominal pain, imaging modalities were employed for disease diagnosis before confirmed lead poisoning diagnosis. Abdominopelvic CT mainly was performed to rule out internal concealment.

Toxicity through ingestion of lead containing paint chips is well reported in children and the paint chips are often visible on abdominal X-rays. The presence of lead particles in the gastrointestinal tract may suggest the diagnosis and prompt further diagnostic or therapeutic measures. McElvaine et al. reported that 26% of their cases with a BLL ≥ 55 µg/dL had positive abdominal X-ray findings while only 2% with BLLs < 55 µg/dL had such a finding [22]. In our study, imaging findings positively related to the BLLs. Patients with BLLs of greater than or equal to 45 µg/dL were more likely to have positive imaging findings with significant P values. Even BLLs of 10 µg/dL and higher (as the indicator of lead exposure in adult patients) were significantly related to both imaging results with a considerable specificity [23]. Interestingly, our study found that in controls (BLL < 45 µg/dL) those with higher BLL levels had more positive imaging results (BLL of 14.4 versus 8 µg/dL). This finding emphasizes the fact that BLLs of 10 µg/dL and higher may accompany with more positive results in imaging

Table 2
Median BLL in abdominopelvic CT, abdominal X-ray and combined imaging results in cases and controls.

Case (n = 79) [IQR] (range)		Control (n = 79) [IQR] (range)		Total (n = 158) [IQR] (range)	
+CT (n = 34)	129 [100.8, 166] (47.3, 248)	**+CT (n = 6)**	13.8 [8.0, 16.9] (1.2, 21)	**+CT (n = 40)**	119.5 [71.8, 155.5] (1.2, 248)
-CT (n = 16)	130 [114, 160] (72, 1124)	**-CT (n = 47)**	8 [5, 15] (1.3, 39)	**-CT (n = 63)**	11 [6.8, 72] (1.3, 1124)
Sig	p = 0.685, MWU	**Sig**	p = 0.275, MWU	**Sig**	p < 0.001, MWU
total (n = 50)	129 [103, 160] (47.3, 1124)	**total (n = 53)**	8.7 [5.3, 15] (1.2, 39)	**total (n = 103)**	33.3 [8, 128] (1.2, 1124)
+X-ray (n = 21)	110 [92, 149] (47.3, 193)	**+X-ray (n = 4)**	15.6 [10.1, 18.8] (8.6, 19.5)	**+X-ray (n = 25)**	100 [75.2, 146] (8.6, 193)
-X-ray (n = 22)	130 [95, 156.2] (42, 205)	**-X-ray (n = 30)**	8 [5.2, 14.2] (1.8, 33.3)	**-X-ray (n = 52)**	18.6 [7.7, 121] (1.8, 205)
Sig	p = 0.576, MWU	**Sig**	p = 0.105, MWU	**Sig**	p = 0.002, MWU
total (n = 43)	126 [95, 151] (47.3, 205)	**total (n = 34)**	8.8 [5.6, 15] (1.8, 33.3)	**total (n = 77)**	73 [9.6, 130.5] (1.8, 205)
+Image (n = 48)	124.5 [97.9, 160.8] (47.3, 248)	**+Image (n = 10)**	14.2 [9.8, 17.5] (1.2, 21)	**+Image (n = 58)**	108.5 [72.2, 150.2] (1.2, 248)
-Image (n = 31)	128 [95, 160] (50.4, 1124)	**-Image (n = 69)**	8 [4.6, 14.2] (1.3, 39)	**-Image (n = 100)**	13 [6.9, 94] (1.3, 1124)
Sig	p = 0.775, MWU	**Sig**	p = 0.047, MWU	**Sig**	p < 0.001, MWU
total (n = 79)	126 [97.4, 160] (47.3, 1124)	**total (n = 79)**	8.7 [5.5, 15] (1.2, 39)	**total (n = 158)**	43.1 [8.7, 126.5] (1.2, 1124)

MVU: Mann Whitney *U* test.

Table 3
Diagnostic characteristics of imaging findings in two cut-offs of BLL > 45 and BLL > 10 μg/Dl.

		Gold standard (BLL > 45 μg/dL)				Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
	Result	positive	negative	Sig*	OR (95%CI)					
CT (n = 103)	positive	34 (68)	6 (11.3)	< 0.001	16.6 [5.9-46.9]	68% (53.3-80.5)	88.7% (77-95.7)	85% (72.3-92.5)	78.6% (69.5-81.6)	78.9 (69.7-86.2)
	negative	16 (32)	47 (88.7)							
X-ray (n = 77)	positive	21 (48.8)	4 (11.8)	0.001	7.2 [2.2-23.8]	48.8% (33.3-64.5)	88.2% (72.6-96.7)	84% (66.6-93.3)	66.2% (54.6-76.6)	66.7% (55.1-76.9)
	negative	22 (51.2)	30 (88.2)							
Both (n = 158)	positive	48 (60.8)	10 (12.7)	< 0.001	10.7 [4.8-23.8]	60.8% (49.1-71.6)	87.3% (78-93.8)	82.8% (72.4-89.8)	69% (62.6-74.8)	74.1% (66.5-80.7)
	negative	31 (39.2)	69 (87.3)							

		(BLL > 10μg/dL)				**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Accuracy (95% CI)**
	Result	**positive**	**negative**	**Sig***	**OR (95%CI)**					
CT (n = 103)	positive	39 (54.9)	1 (3.1)	< 0.001	37.8 [4.9-292.2]	54.9% (42.7-66.8)	96.9% (83.8-99.9)	97.5% (84.8-99.6)	49.2% (42.7-55.8)	63.9% (55.9-71.4)
	negative	32 (45.1)	31 (96.9)							
X-ray (n = 77)	positive	24 (42.1)	1 (5)	0.002	13.8 [1.7-110.4]	42.1% (29.1-55.9)	95% (75.1-99.9)	96% (77.6-99.4)	36.5% (31.1-42.3)	55.8% (44.1-67.2)
	negative	33 (57.9)	19 (95)							
Both (n = 158)	positive	56 (50.5)	2 (4.3)	< 0.001	22.9 [5.3-99.1]	50.4% (40.8-60.1)	95.7% (85.1-99.5)	96.6% (87.7-99.1)	45% (40.2-49.9)	68% (58-76.8)
	negative	55 (49.5)	45 (95.7)							

Table 4
Comparison of imaging findings in Oral opium dependents.

	Oral opium dependents		Sig, 95% CI
Group	*Case (n = 79)*	*Control (n = 11)*	
+CT n (%)	34 (68)	0	p < 0.001
-CT n (%)	16 (32)	8 (100)	
+X-ray n (%)	21 (48.8)	1 (17.7)	p = 0.204, 4.77 (0.5-18)
-X-ray n (%)	22 (51.2)	5 (83.3)	
+Image n (%)	48 (60.8)	1 (9.1)	p = 0.002, 15.48 (1.89-127)
-Image n (%)	31 (39.2)	10 (91.9)	

studies.

Opium use and concomitant overdose is common in Iran [15,24,25]. Chia et al described the first report of opium contaminated with lead in 1973 [26]. In the recent decades, researchers have reported patients poisoned by lead-contaminated opium [10,13,27–29]. Lead-contaminated opium as a source of lead poisoning have been previously reported [20,21,30].

Previously reported radiologic findings in lead intoxication mainly focused on bone and brain pictures and not gastrointestinal imaging [12,31]. In cases of paint chips in the intestine, McElvaine et al. reported dense opaque particles in abdominal radiographs [23]. However, we found that in opium-related lead intoxication, lead particles dispersed in the bowel lumen after the opium had dissolved in the intestines. Although imaging alone cannot determine the nature of foreign material, the configuration of multiple uniform tiny dense particles in the gastrointestinal tract in the presence of lead poisoning symptoms is suggestive of lead intoxication.

Compared to abdominal X rays, CT proved more predictive of higher BLLs (Fig. 4). These imaging studies were performed for the indications discussed by other physicians and surgeons in emergency department.

Table 5
Logistic regression analysis for predicting Imaging studies.

Imaging Technique	Independent variable	Beta	SE of beta	OR (95% CI)	Model type, significance and Nagelkerke R Square
Positive Abdominopelvic CT (n = 40)	BLL > 45 (Yes vs. No)	3.67	0.69	39.46 (10.21, 159.60)	Stepwise, < 0.001, 0.514
Positive Abdominopelvic X-ray (n = 25)	BLL > 45 (Yes vs. No)	2.25	0.76	9.51 (2.15, 49.09)	Stepwise, 0.003, 0.383
	BUN (mg/dL)	−0.52	0.21	0.95 (091, 0.99)	
Positive Imaging (n = 53)	Constipation (Yes vs. No)	1.36	0.69	3.91 (1.02, 15.03)	Stepwise, < 0.001, 0.435
	BLL > 45 (Yes vs. No)	2.72	0.51	15.12 (5.52, 41.35)	

CI: confidence interval, SE: standard error.

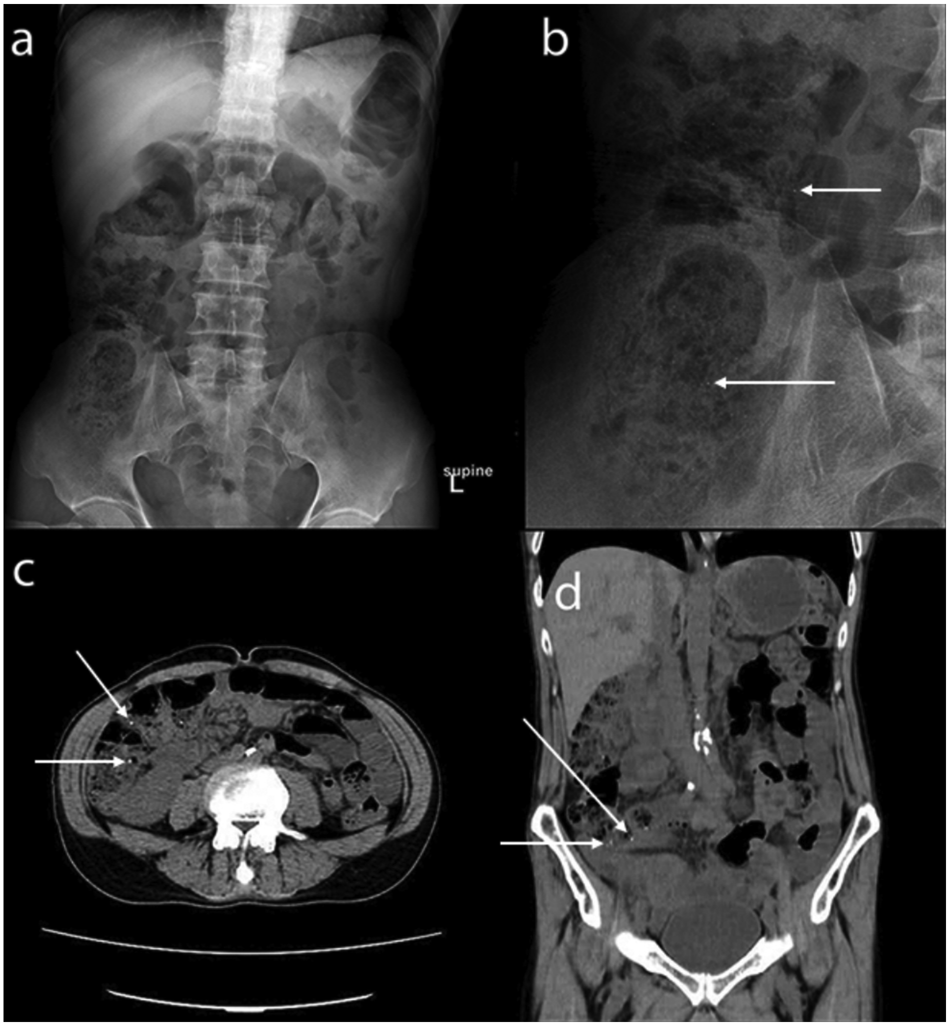

Fig. 4. Plain abdominal X-ray (a) which may be interpreted as normal; however, after focusing on the right lower quadrant region (b) tiny dense foci are detected (arrows). The findings are confirmed in non-enhanced abdominal CT scan in axial (c) and coronal (d) views which demonstrate tiny hyperdense foci, some of them marked by arrows.

Our study has several limitations. Although the best control group for our cases were non-lead-poisoned opium patients, due to ethical limitations, we could not recruit such patients. In fact, ethically, we could not perform abdominal CT or X-ray in patients who had no symptoms of abdominal involvement and had referred only for treatment of other poisonings including opium overdose. We selected our controls from those with abdominal problems who did not have lead toxicity and who might not be opium users. Even with data selection, 11 patients in the control group were determined to be oral opium abusers. A subgroup analysis performed between these 11 patients and cases showed that none of the opium patients in the control group had positive CT and only one had positive X-ray, merely emphasizing that irrespective of being an oral opium user, higher frequency of positive imaging shows a 15.5- fold risk of being lead-intoxicated.

We performed stepwise forward logistic regression and showed that BLLs higher than 45 μg/dL and constipation were the factors with significant results ($P < 0.001$). As it is common in opioid-dependent patients, we found constipation to be the best variable predicting a positive CT [30]. Because constipation may keep lead particles for a longer than typical period of time, the particles are more easily identifiable particularly when using CT scan. However, only BLLs of 45 μg/dL and higher significantly predicted a positive CT with an outstanding odds ratio of 39.5.

As illustrated in Table 2, BLLs higher than 45 were statistically significant in the association of positive imaging (CT, X-ray, and combined). BLLs above 10 μg/dL showed significant value in predicting positive imaging modalities. In fact, when a case presents with signs and symptoms of lead toxicity, a CT positive for multiple metallic densities may predict BLL higher than 10 μg/dL with a specificity of 96.9% and PPV of 97.5%. These numbers decrease to 88.7% and 85% with BLLs higher than 45 μg/dL. This level is acceptable and we think that for patients with typical signs and symptoms of lead toxicity and a positive CT, chelation therapy can be initiated if BLL is not available. CT may be a useful tool for opium patients or simply for radiologists to consider lead exposure.

Study limitations included self-reporting of symptoms, imaging quality and often unknown timing of ingestion.

The strength of this study is the sample size and prospective data collection. To potentially detect lead poisoning in opioid patients, we emphasize the efficacy of imaging modalities, while awaiting blood test results. The radiodensities described on both CT and X-ray are nonspecific and can represent other elements (i.e. barium, bismuth), and even a dirty cassette may produce such an appearance. Therefore, the presence of demonstrated radiodensities based on imaging alone, without clinical characteristics of lead poisoning, it may be unwise to initiate chelation. Considering the chemical process of producing opioids from opium, other opioids can be polluted as well [32]. Finally, the study population of both cases and controls comes from a unique toxicology center, which may introduce referral bias into to data.

5. Conclusion

For suspected cases of lead toxicity in male opioid users who refer with abdominal pain, constipation, and anemia, we conclude that if BLL is not readily available, a positive imaging study (CT > plain x-rays) can guide practitioners to consider lead exposure, and possibly start decontamination and chelation. Identification of lead exposure in opioid abusers is recommended. This may help early on-time treatment in patients at high risk of lead-induced serious complications including encephalopathy living in underdeveloped or developing countries where atomic absorption technique is not readily available.

Conflict of interest

None.

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Appendix A. Supplementary data

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