Review of Cases of Lead Poisoning From Opium Abuse In IRAN

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Running title: Review of lead poisoning from opium abuse

Summary

Lead toxicity has been recognized form antiquity and still exists today**.** Today opium is the new source of lead exposure, There are some reports of lead poisoning with opium, from Iran**.** We find 6 reports (9 cases) about this subject. All of these patients were Iranian and addicted to opium. The ages of all cases were 25- 68 years old (mean=40.9 ±14.07). The most common symptoms were abdominal pain (100%) and nausea (4 cases of 9 (44.4%)) .The most signs were abdominal tenderness (100%) and icter (4 cases of 9 (44.4%))and neurologic problem(3 cases of 9 (33.3%)). All of them reported anemia and elevated liver enzymes (ALT AND AST) but none of them reported any renal function abnormalities. Their manifestations and abnormalities in lab tests were relived after about 4-15 days and about one month of starting chelating treatment, respectively, although one cases did not respond to treatment and died. Some reasons of cause of opium lead-contamination are : the addition of lead for increasing the weight of the opium by salesmen, and be due to the processing or preparation of opium. Another reason may be due to presence of lead miners located near to the opium cultivation's lands. all of these reports are male and we cannot find any reports of women. We suggest higher opioid consumption in men than in women is reason. Although all of the reported cases had pbl> 20 µg/dL, all of them were reported with normal vital signs and none reported any or high blood pressure. It may be due to the vasodilatoric effect of opium (morphine). In conclusion, lead poisoning often goes unrecognized for long periods of time due to a low index of suspicion, but may be fatal. Therefore, it should always be considered in the differential diagnosis of unexplained anemia or abdominal symptoms, especially in opium addicts.

Introduction

Lead is a silvery -gray soft metal that is widely distributed in environment. Inorganic lead is greatly water soluble and widely used in several industries such as for pigments associated with paint and for gasoline additives [1]. It is a toxic metal that affects many organ systems and functions in humans such as the central and peripheral nervous, renal, vascular, reproductive, hematologic, skeletal, endocrine and gastrointestinal systems [1-3]. This medical condition is also known as saturnism or plumbism dates back to antiquity [1, 4, 5]. It can also be present with nonspecific signs and symptoms such as abdominal pain, constipation, irritability, and anemia in show itself in very different degrees of severity and appearance[6-9].

Lead toxicity can be caused by occupational or environmental exposure to sources of (in)organic lead. The most common sources are lead-containing paint, drinking water, lead pipes from public water supply, Asian herbal remedies, lead-glazed ceramics and lead shot games [4, 5]. Owing to the increasing levels of safety at work, the incidence of occupational lead poisoning has decreased and new forms of non-occupational poisoning have emerged [10]. Lead poisoning due to opium addiction has been reported in a few studies in Iran [10-16] .

The Middle East is the main way of opium transit and trafficking from Afghanistan to the rest of the world. Also, about 1-4 million addict are in Iran and opium addiction is one of the most prevalent forms of drug addiction in Iran, and is a matter of health significance to this country [12, 17, 18]. In this manuscript we review the case reports of lead poisoning due to opium addiction that were reported in Iran, as a new source of lead toxicity.

Cases

We find 6 reports (9 cases) about this subject. All of these patients were Iranian and addicted to opium as ingested or inhaled. The authors failed to reveal any other source of lead exposure except opium. All of them were male and we did not find any report about children or women. All cases that used opium were in Iran, Although one of them immigrated to the United States (he contracted his problem after returning to U.S. from Iran.) [11].

Case 1:

A 25 years old man was presented with abdominal pain, nausea, vomiting, lost about 8 kg of weight, malaise, weakness, excess sweating, darkened urine color and generalized bone pain and jaundice. He had six years history of addiction to oral and inhalation forms of opium. Physical examination showed pallor and icter and, bluish pigmentation of the gum tooth. Other exam was normal. Laboratory tests were indicative increasing liver enzymes (ALT: 118 U/L, AST: 93 U/L) and billirubin (4.0 mg/dL) and normocytic-hypochromic anemia without autoimmune origin . Other laboratory tests were normal .The lead serum level was 350 mcg/dl. His symptoms and laboratory tests were relived after 2 weeks and 45 days of treatment, respectively [12].

Case 2:

A 34-year-old driver man was hospitalized due to ten-day recurrent bouts abdominal pain, nausea and vomiting. The patient was addicted to opium (ingestion). On physical examination the patient had pain without guarding over the abdomen. His vital signs, neurologic and other examinations were normal. Laboratory tests revealed normochromic- normocytic anemia (hemoglobin:11 g/dL), basophilic stippling of erythrocytes, elevated liver enzymes (ALT: 83 U/L, AST: 176 U/L) and total bilirubin (2.1 mg/dL). Other laboratory tests such as viral and autoimmune hepatitis and renal function tests were normal .He had an elevated blood lead level (95 µg/dL). Symptoms improved after a five-day course of treatment with calcium EDTA and discontinuation of selfingested opium. Laboratory data were normal after one month [10].

Case 3:

A 57-year-old business man (peddler) was admitted to the hospital for a 30 day progressive and diffuse colicky abdominal pain, nausea and severe constipation. He was addicted to opium (ingestion) and cigarette smoking. On physical examination he had pain without guarding over the abdomen. Laboratory investigations were as follows: hemoglobin 10.5 g/dL; MCV 82 fl ; ALT 87 U/L and AST 90 U/L. Other laboratory tests such as viral and autoimmune hepatitis and renal function and bilirubin tests were normal. His lead serum level was 81 µg/dL. The patient's symptoms improved after four days of treatment with calcium EDTA and discontinuing ingestion of the opium. Laboratory data were normal after 3 weeks [10].

Case 4:

A 45-year-old laborer, was presented with repeated attacks of severe two weeks epigastric and periumbilical pain. He had a history of opium ingestion and had increased his opium intake in order to decrease his pain. On physical examination he had pain with mild tenderness over the abdomen and his vital signs, neurologic and other examinations were all normal. Laboratory tests showed normochromic-normocytic anemia (hemoglobin 9 g/dL), elevated liver enzymes (ALT: 80U/L, AST: 67 U/L), total bilirubin (1.4 mg/dL) and normal results for other tests. His lead serum level was 37.5 µg/dL. Symptoms responded after four days discontinuation of opium intake. There was no need to use chelating agents in this patient. Laboratory data were normal after one month [10].

Case 5:

A 40-year-old man, immigrant from Iran, to United State who was admitted to the hospital with severe, constant, upper abdominal pain. His complaints had started following a short stay in Iran. He also had exacerbating-remitting multiple sclerosis, for which he received weekly interferon-beta injections. Due chronic pain he also used Iranian opium regularly. Physical examination revealed a sweating, hemodynamic stable, non-icteric patient in evident pain. He had decreased bowel sounds and tenderness of right upper quadrant of abdominal without guarding. Laboratory findings included a normocytic anemia (hemoglobin 5.7 mmol/L; MCV 84 fl) with basophilic stippling , and elevated liver function tests: AST 66 U/L (N 0-35), ALT 92 U/L (N 0-45), gamma-GT 729 U/L (N 0-40).Other laboratory test such as renal function and viral and autoimmune hepatitis was normal. The serum lead concentration was 860 µg/L. The patient's symptoms improved after 14 days of treatment with calcium EDTA and dimercaprol followed by oral succimer . The patient was lost for follow-up [11].

Case 6

A clerk forty years male was admitted to hospital with paresthesia in upper and lower extremities. He had suffered headache, nausea and abdominal pain since one month earlier. He developed weakness over his lower extremity which progressed to upper arms, and admission to intensive care unit. His vital signs were normal. Physical examination revealed diffuse abdominal tenderness with no guarding, icitric sclera. Neurologic examination showed decreased deep tendon reflexes in lower extremity (+1) and muscle strength in proximal and distal part of extremity were 2/5 and 3/5 respectively. During admission, he developed quadriplegia and respiratory muscles weakness progressive to respiratory failure, without any sensory involvement. Laboratory investigation showed; anemia (Hb 7.7 g/dl) with

basophilic stippling, total bilirubin (4.2 mg/dl) and slightly elevated liver function test. Blood lead level was >200 µg/dl. The patient's symptoms improved after 10 days of treatment with calcium EDTA and dimercaprol followed by oral succimer .Upon discharge from the ICU all laboratory tests were normal and he was referred to a rehabilitation center[13].

Case 7:

He was a 27 year old opium addict worker man, who had suffered colicky abdominal pain, weakness and constipation since two months. During hospitalization, patient showed icter and a reduction in the level of consciousness (delirium and hyperirritability) and reoffered to the ICU. On physical exam revealed normal vital signs, generalized abdominal tenderness without guarding. Neurologic exam revealed tremor, hyperirritability and delirium. Motor and sensory exam were normal. Lab tests revealed anemia of Hb 9g/dl, total bilirubin 6.5 mg/dl, and an increase in liver enzymes ALT 138 U/L, AST 102 U/L. Blood lead level was 154 µg/dl. Symptoms gradually improved after a five days of treatment[15].

Case 8:

(Father of case 7) He was a 68 year old worker man who had suffered abdominal pain, icter, insomnia, weight loss and

anorexia since one month. After one week of admission occurred loss of consciousness, confusion and coma. He had diabetes mellitus, cigarette smoking and opium addiction. On physical exam vital signs were normal, upper and lower extremities were paralyzed, atonic with absent deep tendon reflexes. Lab tests revealed anemia of Hb 6.5 g/dl, elevated liver enzymes ALT 40 u/l, AST 88 u/l and total bilirubin 6.5 mg/dl, with normal viral test. Lead level in whole blood was 180 mg/dl. Patient did not respond to a five day treatment with BAL and CaNa2 + EDTA, and died [15].

Case 9:

A 32-year-old man presented with five weeks of constant diffuse abdominal pain and constipation, without loss of appetite , nausea or vomiting. He was addicted to opium, and stated that he ingested about 20 grams per day. His vital signs were stable. He had dark line along the gingival margin. Abdomen revealed mild tenderness to deep palpation of the lower abdomen, without rebound and guarding. Neurological examination was normal .Laboratory investigation showed; anemia (Hb 9.8 g/dl) with basophilic stippling, slightly elevated liver function tests, ALT 72 u/l, AST 95 u/. Other laboratory tests such as renal function and viral and autoimmune hepatitis were normal. Whole blood lead level was 50 µg/dL. The patient was put on chelation therapy with (DMSA). His abdominal pain subsided over the next week. Marked resolution of all signs and symptoms occurred by one month follow up[16].

Discussion

The ages of all cases were 25- 68 years old (mean=40.9 ±14.07). The most common symptoms were abdominal pain (100%) and nausea (4 cases of 9 (44.4%)) .The most signs were abdominal tenderness (100%) and icter (4 cases of 9 (44.4%))and neurologic problem(3 cases of 9 (33.3%)). All of them reported anemia and elevated liver enzymes (ALT AND AST) but none of them reported any renal function abnormalities . All of them had negative laboratory result of viral and autoimmune hepatitis.

Their manifestations and abnormalities in lab tests were relived after about 4-15 days and about one month of starting chelating treatment, respectively, although one cases did not respond to treatment and died.

Lead toxicity has been recognized for thousands of years and still exists today. Lead exposure can occur in numerous work settings [2, 8, 19]. Today opium is the new source of lead exposure. Lead poisoning by injection or inhalation of heroin adulterated with lead has been recognized since 1989 and there were few reports of contaminated heroin and acute lead poisoning as a result of self-injection of lead and opium pills, crushed and suspended in water[20-26]. Today there are some reports of lead poisoning with opium, not only from Iran[10-16] but also from other countries such as China [21].

Contamination of opium with lead is confirmed in some studies on samples of opium that were seized by the Police Department of Iran or use by addicts [10, 16, 17, 27]. The cause of this contamination is unknown, but some reasons may be present. The first is the addition of lead for increasing the weight of the opium by salesmen or smugglers, and the second may be due to the processing or preparation of opium. Another reason may be due to the location of opium cultivation. The pattern of additional materials to opium are as a "chemical fingerprint " of preparing the geographical location [27]. We supposed that the high concentration of lead in samplings of opium in two studies[17, 27] due to presence of lead miners located near to the opium cultivation's lands. The United Nations Office on Drugs and Crime reported in the Afghanistan Opium Survey 2007 that while over 80% of Afghanistan's opium is cultivated in the Southern regions, the largest increases in yields have been in the Central and Eastern regions (123% and 23%, respectively) [28]. Also, the distribution of Afghanistan's lead miners are in the center of this country [29], and it can describe the presence of new cases of lead poisoning from opium.

The most prevalent form of opium consumption in Iran is inhalation[17]. Pulmonary absorption is more efficient than gastrointestinal absorption as 30-40 percent of inhaled versus 10-15 percent of digested lead[1, 4, 5, 30, 31]. So the risk of lead poisoning of Iranian addicts are higher. It must be noted that the WHO recommended that a person with a body weight of 68 kg can intake 240 µg lead/day as Tolerable Daily Intake (TDI) ,and 6-18 µg lead/day in a 10 kg child [32, 33]and GI absorption of lead is greatest in infancy as they can absorb up to 50 percent of the ingested lead. [1, 4, 31] according to presence of about 2-325 PPM lead in the samples of opium [16, 17, 27], if an addict consumes approximately 20 g of opium daily (some addicts consume up to 100 g/day) he/she will receive 6% till more than 100% of lead TDI, , and if a 10 kg child addict consumes approximately 1 g of opium daily he/she will receive at least 1 µg of lead daily up to 3 fold of TDI [17, 27]. This data confirm by Salehi H.et al report. They showed 40.9% of opium addict men had blood lead level equal or greater than 25µg/dL. In this report there was correlation between blood lead level and amount of opium ingestion , not duration[34].

Although all of these reports are from males and we cannot find any reports of children or women, the diagnosis of lead toxicity due to opium addiction in children is more important than with adults. Especially the majority of addicted children were born by addicted mothers and they have been addicted

since their birthdays. It is more important when we know that the bone lead of pregnant mothers is readily transferred to the fetal skeleton during pregnancy[5, 35].

Morphine is more potent in women than in men, and the onset/offset of morphine is slower in women than in men[36]. In addition, women experience more side effects of morphine (such as nausea,…) and with greater intensity [36]. Therefore opioid consumption is higher in men than in women and this may be one reason of lack of lead poisoning report due to opium in women

It is known that elevated blood levels of lead(pbl) (20-29 μg/dL) correlate with significant increases in all-cause circulatory and cardiovascular mortality [37]. Several clinical trials and population studies of occupationally exposed groups have shown that lead exposure correlates with increased incidence of hypertension, cerebrovascular disease and cardiovascular disease[4, 38-40]. There is substantial evidence that long-term, low-level exposure to lead can contribute to hypertension in both animals and humans[5]. Although all of the reported cases had pbl> 20 μg/dL, all of them were reported with normal vital signs and none reported any hypertension or high blood pressure. It may be due to the effect of opium (morphine) on the decreasing of blood pressure [41].

Studies on autopsy liver of Pb-exposed humans indicate that liver tissue is the largest repository of Pb [42]. Although lead poisoning can cause liver damage ranging from increased liver enzymes to hepatic failure, mechanisms involved in lead hepatotoxicity remain to be elucidated [20, 42-44]. The major concepts is attributed to their ability to generate reactive oxygen species and cause oxidative stress[1, 42, 45]. Shalana, showed that lead acetate ingestion (500 mg/kg diet) induced a significant elevation of serum ALT, AST, GGT and ALP levels after 14 days of treatment of rats [46]. Studies of evaluation Pb exposure and liver injury by measuring serum enzymes (i.e., alkaline phosphatase and lactate dehydrogenase) reported different results. Al-Neamy reported 100 male workers who had significantly higher serum levels of alkaline phosphatase and lactate dehydrogenase when their mean blood Pb levels were 78 mg/dl [47] . But Hsiao were not found Such alterations in a longitudinal study of battery workers whose mean blood Pb levels ranged from 60 mg/dl in 1989 to 30 mg/dl in 1999[48]. But AST and ALT were elevated in all of cases of lead poisoning due to opium use. This increasing of liver enzymes may be due to co-toxicity of lead and other additive materials to opium such as Cadmium or Arsenic [49, 50]. The course of the serum values of the liver enzymes in these patients suggests the reversibility of this process.

Lead nephropathy has been well documented in occupationally exposed workers. It manifests as proximal tubular damage, glomerular sclerosis and interstitial fibrosis. Common signs include proteinuria, impaired transport of glucose and organic anions, and a lowered glomerular filtration rate (GFR) [51]. Historically, renal insufficiency was found in acute lead toxicity in high PbBs >80 μg/dL.[4, 52]. Although eight of these cases had PbBs >80 μg/dL, the authors did not report any renal insufficiency or renal laboratory test abnormalities. It is important to note that the BUN and creatinin are not sensitive indicators of renal damage, since these tests do not rise until the kidney function is over 50 percent lost [53] and the authors did not report 24 hours urine collection tests of these patients .

In conclusion, lead poisoning often goes unrecognized for long periods of time due to a low index of suspicion, but lead poisoning may be fatal. Therefore, it should always be considered in the differential diagnosis of unexplained anemia or abdominal symptoms, especially in opium addicts. Also, it is recommended to evaluate the concentration of lead in the sera of opium addicts, especially in children.

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