Extra ordinary high blood lead levels in Mashhad, Iran: a one-year study in a referral center

ABSTRACT

Introduction: Lead is a heavy metal with vast usage in the industry. Lead toxicity affects any organ in the body. It causes various clinical presentations, which leads to diagnostic complexity. Regarding recent increased observation of cases with lead toxicity in our center, we aimed to evaluate the frequencies of lead toxicity in patients referred to Imam-Reza Hospital’s laboratory and find a possible relationship between the blood lead level (BLL) and hematological and biochemical tests.

Methods: From 2016 to 2017, the patients referred to Imam-Reza hospital’s laboratory to detect BLL enrolled in the study. Among them, 254 adult cases with BLLs≥10 µg/dl were selected. Complete blood counts and peripheral blood smear were done. Other lab data were extracted from hospital files.

Results: The mean BLL of 1649 participants was 59.11±116.25 µg/dl, ranging from 0 to 1580. Sixty nine percent of them had lead toxicity. Eighty-one percent (n=1341) of patients were males and 18.7% (n=308) were females. In 254 selected cases, the mean BLL was 138.17±189.98 µg/dl. There were significant inverse correlations between BLL and red blood cell counts, hemoglobin, mean cell hemoglobin, total iron-binding capacity, target shape and basophilic stippling, as well as positive correlations between BLL and white blood cell counts, red cell distribution width, neutrophil counts and iron.

Conclusion: Lead toxicity seems to be more frequent than it is expected. Patients with unexplained anemia with increased iron and decreased total iron-binding capacity are better to be evaluated for BLL.

Introduction

Lead is a heavy metal that was widely used in the industry because of its special chemical and physical properties including malleability, resistance to corrosion and poor conductivity (Wani et al., 2015). Lead toxicity has affected individuals since historical times. It was postulated that the Roman Emperor collapse may be a consequence of dementia attributed to lead-containing wines (Wani et al., 2015). Lead toxicity affects any organ in the body including central nervous
system, blood, gastrointestinal tract and reproductive system. Consequently, it can be presented with non-specific signs and symptoms such as nausea, abdominal pain, weakness, neuropathy and even coma as well as unconsciousness (Gidlow, 2015; Wani et al., 2015). Therefore, the diagnosis may be missed until severe toxicity occurs. Lead can cause sideroblastic anemia. Sideroblastic anemias are defined by an increase in marrow sideroblasts as a result of some disruption in iron incorporation to the hemoglobin (McPherson, 2017). Through interfering with some enzymes involved in the biosynthesis of heme as well as enzymes work in maintaining red blood cell (RBC) membrane integrity, lead can cause anemia by reduction in production and hemolysis (Halmo and Nappe, 2019). The anemia of lead poisoning is mostly of normochromic normocytic and sometimes hypochromic microcytic (Gidlow, 2015). Lead is stored in the kidney and liver. It can result in a reduction of renal glomeruli as well as renal tubular damage (Kshirsagar et al., 2015; Buser et al., 2016; Nakhaee et al., 2019). In addition, lead can cause oxidative liver damage (Dadpour et al., 2016; Nakhaee et al., 2019).

The limitation of lead use in the industry has decreased the prevalence of lead toxicity. Lead-based paint and lead-contaminated dust in old buildings are the main sources of lead toxicity in children; other sources include some occupations as well as contaminated air or water (Gidlow, 2015; Wani et al., 2015). Lead contaminated opium was recently introduced as a new source of lead toxicity in Iran and some authors alarmed about the lead outbreak between opium users (Meybodi et al., 2012; Hayatbakhsh et al., 2017; Ghane et al., 2018; Karrari et al., 2012). Khorasan province sharing a common border with Afghanistan, one of the major opium producers, suffers widely from opium related health problems. We evaluated the frequency of lead toxicity in patients referred to Imam Reza university hospital’s central laboratory, Mashhad, Iran and searched for correlations between patient’s blood lead level ( BLL) and their hematological and biochemical tests. Imam Reza university hospital is the biggest general hospital in the east of Iran which is the referral hospital in many fields, including toxicology.

Material and methods
The study was conducted at Imam Reza university hospital, Mashhad University of Medical Sciences, Mashhad, Iran. Between September 2016 and September 2017, all patients referred to the Imam Reza university hospital’s central laboratory, Mashhad, Iran for detecting BLL enrolled in the study. The study protocol was approved by Research Ethics Committee in Mashhad University of Medical Sciences (IR.MUMS. fm.REC.1396.162).

The age, sex and BLL of patients were extracted from hospital files. The BLL was detected using PerkinElmer atomic absorption spectrophotometer (Perkin-Elmer AAnalyst, USA). The BLL of 10 µg/dl or more was regarded as lead toxicity (Wani et al., 2015). Among the patients, 254 adult cases with BLL ≥ 10µg/dl were selected non-randomly. Complete blood counts (CBC) and peripheral blood smear (PBS) were done on the same blood sample used to detect BLL. The CBC was done using Sysmex KX21 hematology analyzer (Sysmex Co., Japan). The PBS stained using the Geimsa method (Kuhlmann, 2018). An experienced technologist evaluated RBC morphology, including hypochromia, microcyte, macrocyte, target shape and basophilic stippling. The presence of each morphologic change was assessed according to the ICSH guideline (Palmer et al., 2015). Biochemical lab data of cases including blood urea nitrogen (BUN), creatinine (Cre), aspartate amino transferase (AST), alanine amino transferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALK), iron and total iron-binding capacity (TIBC) were extracted from hospital electronic files. Biochemical lab tests were done using BS 300 autoanalyzer (Biotecnica instruments S.P.A., Italy). Finally, correlations between BLL and CBC, PBS findings, as well as other lab data were evaluated. Anemia was defined as hemoglobin (Hb) levels less than 12.3g/dl and 14g/dl in females and males, respectively. As RBC counts as well as Hb and hematocrit (Hct) show different reference levels in males and females, these parameters were separately evaluated in two sexes. A WBC counts ≥11000/µl was considered leukocytosis, whereas WBC counts ≤4400/µl was defined as leukopenia (McPherson, 2017).

Statistical analysis
Data analysis was performed using SPSS 11.5 software (SPSS, Chicago, IL). As the BLL of patients did not show normal distribution, non-parametric tests were employed. Spearman’s correlation was used to find
correlations between BLL and quantitative variables, including CBC parameters, BUN, Cre, ALT, AST, LDH, ALK, iron and TIBC. To find any association between BLL and PBS findings, the Mann-Whitney test was employed. The $P$ values less than 0.05 were considered statistically significant.

Results

From September 2016 to September 2017, 1649 cases were referred to Imam Reza hospital’s central laboratory to detect BLL. The demographic characteristics of the patients are presented in Table 1. Most patients were males (81.3%, n=1341). The patients’ ages ranged from 0 to 92 years, with a mean $±$ SD of 45.61±20 years. Their mean $±$ SD of BLL was 59.11±116.25 µg/dl, ranging from 0 to 1580µg/dl. Figure 1 shows the distribution of different levels of blood lead in studied cases. According to a cut-off level of 10µg/dl, 69.1% (n=1140) of patients showed toxic levels of lead in their blood. The BLL in 15% (n=247) was above 100µg/dl and 5 patients had BLLs of more than 1000µg/dl.

There was a statistically significant but weak correlation between age and BLL ($P=0.002$, Spearman’s correlation coefficient: 0.09). The differences between BLL in men (mean$±$SD: 60.86±117.8 µg/dl) and women (mean$±$SD: 51.70±109.18 µg/dl) were statistically significant ($P<0.001$). In 254 selected cases with BLL $\geq$10µg/dl, the mean$±$SD of BLL was 138.17±189.98 µg/dl. The results of the CBC and biochemical tests of these patients, as well as correlations between BLL and lab results are summarized in Table 2. There were significant inverse correlations between BLL and RBC count, Hb, Hct, mean cell hemoglobin (MCH) and TIBC (Table 2). Besides, significant positive correlations were found between BLL and WBC count, red cell distribution width (RDW), absolute neutrophil counts and iron. Two hundred six patients (81.1%) were anemic. Thirty-eight cases (15%) showed leukocytosis, whereas 17 (6.7%) exhibited leukopenia.

As RBC counts, as well as Hb and Hct show different reference levels in males and females, these parameters were separately evaluated in two sexes and their correlation with BLL was re-evaluated (Table 3). There were significant correlations between BLL and

| Variable name    | Categories | Mean±SD, or n(%) |
|------------------|------------|------------------|
| Age (years)      | -          | 45.61±20         |
| Sex              | Males      | 1341 (81.3%)     |
|                  | Females    | 308 (18.7%)      |
| BLL (µg/dl)      | -          | 59.11±116.25     |

BLL: blood lead level

**FIGURE 1.** Blood lead level of the studied cases. Four cases showed BLLs of more than 1000µg/dl.

**TABLE 1:** The demographic data of patients
RBC count, Hb and Hct only in men. The results of the morphologic evaluation of PBS are shown in Table 4. About 88% of patients had abnormal morphology. There were significant associations between higher BLLs and the presence of hypochromia, anisocytosis, target shape, as well as basophilic stippling (P values: 0.013, 0.006, 0.001).

| Variable name          | Mean±SD  | Correlation | P value |
|------------------------|----------|-------------|---------|
| WBC Counts (×10³ /µl)  | 8.56±3.74| 0.39        | <0.001  |
| RBC Counts (×10³ /µl)  | 4.04±0.76| -0.31       | <0.001  |
| Hemoglobin (g/dl)      | 11.31±2.53| -0.3       | <0.001  |
| Hematocrit (%)         | 35.61±7.63| -0.24      | <0.001  |
| MCV (fL)               | 88.35±8.42| -0.08      | 0.21    |
| MCH (pg)               | 27.83±2.60| -0.14      | 0.02    |
| MCHC (g/dl)            | 31.44±1.64| -0.12      | 0.06    |
| RDW (%)                | 15.63±2.87| 0.26       | <0.001  |
| Platelet count (×10³ /µl) | 271.55±97.95| 0.08    | 0.27    |
| PDW (%)                | 14.88±2.41| 0.74       | 0.32    |
| MPV (fL)               | 11.14±1.04| 0.49       | 0.51    |
| P-LCR (%)              | 34.54±8.52| 0.06       | 0.46    |
| ANC (×10³ /µl)         | 5.40±3.33 | 0.38       | 0.001   |
| ALC (×10³ /µl)         | 2.14±1.17 | -0.06      | 0.45    |
| BUN (mg/dl)            | 15.17±7.23| 0.02       | 0.9     |
| Cre (mg/dl)            | 0.98±0.32 | -0.09      | 0.61    |
| AST (U/L)              | 58.47±80.20| 0.1       | 0.45    |
| ALT (U/L)              | 54.51±54.41| 0.12      | 0.39    |
| LDH (U/L)              | 633.27±625.93| -0.23    | 0.21    |
| ALK (U/L)              | 278.18±190.72| -0.24    | 0.16    |
| Iron (µg/dl)           | 88.16±53.08| 0.34      | 0.04    |
| TIBC (µg/dl)           | 315.71±72.28| -0.38    | 0.03    |

MCV: mean cell volume, MCH: mean cells hemoglobin, MCHC: mean cells hemoglobin concentration, RDW: red cells distribution width, PDW: platelets distribution width, MPV: mean platelets volume, P-LCR: platelets large cell ratio, ANC: absolute neutrophil counts, ALC: absolute lymphocytes counts, BUN: blood urea nitrogen, Cre: Creatinin, AST: aspartate amino transferase, ALT: alanin amino transferase, LDH: lactate dehydrogenase, ALK alkaline phosphatase, TIBC: total iron binding capacity.

| Variable name         | Male    | Female  | Sex | Mean±SD  | Correlation | P value |
|-----------------------|---------|---------|-----|----------|-------------|---------|
| RBC counts (per µl)   | 4.03±0.77 | 4.13±0.76 | Male | -0.32    | <0.001      |
|                       | 11.30±2.57| 11.35±2.37| Male | -0.3       | <0.001  |
|                       | 35.31±7.13| 37.46±9.99| Male | -0.25   | <0.001  |
|                       | 37.46±9.99| 37.46±9.99| Female| -0.2   | 0.25    |
Discussion

This study evaluated the mean BLL of 1649 patients referred to Imam Reza University Hospital, Mashhad, Iran and found a mean ± SD of BLL was 59.11 ± 116.25 µg/dl. About 69% of patients showed BLLs above the toxic level (10 µg/dl). These results are much higher than the mean BLL of the population in Mashhad (Farhat et al., 2006; Deldar et al., 2008; Mansoori et al., 2009). In a study of 80 mothers in Mashhad, mean BLLs of 10.49 and 12.46 were reported for two groups based on their infants' birth weight (Mansoori et al., 2009). Other studies reported mean BLLs of 12.19 and 16.38 for children aged from 1 to 7 years living in Mashhad (Farhat et al., 2006; Deldar et al., 2008). Even in the industrialized, polluted city of Tehran, reported BLLs are much lower (Farzin et al., 2008; Hassanian-Moghaddam et al., 2018). Farzin et al. (2008) in a study of 101 volunteers resident in Tehran, Iran, found a BLL of 12.37 ± 5.64 µg/dl. Besides, occupationally exposed workers in Mashhad did not show such high BLLs (Balali-Mood et al., 2010; Keramati et al., 2010). Keramati et al. (2010) in a study on 105 battery manufacturing workers, reported a mean BLL of 32.27 ± 13.7 µg/dl. Balali-Mood et al. (2010) reported a mean BLL of 52.05 ± 32.32 µg/dl in 108 workers of Mashhad traditional tile factories. In addition, the participants in this study were not occupationally exposed workers referring for their routine checkups. Lead contaminated opium was recently introduced as a new source of lead toxicity in Iran (Meybodi et al., 2012; Hayatbakhsh et al., 2017; Ghane et al., 2018). Hayatbakhsh et al. (2017) reported an increase in opium-related lead poisoning in the Kerman province and alarmed this emerging lead source's awareness. Ghane et al. (2018) reported an outbreak of lead toxicity in Tehran. BLLs of 37.15 ± 22.75 to 57.04 µg/dl in opium addicts are reported by some authors (Amiri and Amini, 2012; Ahmadinejad et al., 2019; Froutan et al., 2011). The reported BLLs in addicts are in line with our results. Furthermore, according to the feedback from the clinicians, many of our studied cases were opium addicts. Therefore, the lead contaminated opium may be the source of the extraordinary high BLLs observed in the present study. Further studies exploring the BLL as well as possible causes of lead toxicity (e.g. addiction) simultaneously, are needed to confirm this claim. The highest BLL found in the present study was 1580 µg/dl. Even in symptomatic patients who are reported as cases, BLL was ranging from 50 to 323 µg/dl (Mohseni Masoodi et al.; Beigmohammadi et al., 2008; Fatemi et al., 2008; Jalili and Azizkhan, 2009; Moharari et al., 2009; Verheij et al., 2009; Salman-Roghani and Foroozan, 2011; Soltaninejad et al., 2011; Meybodi et al., 2012; Alinejad et al., 2018; Soltaninejad and Shadnia, 2018). Regarding the possible role of opium addiction as the cause of lead toxicity in this study, the unexpected extraordinary BLLs could be related to the location of Khorasan province at the common border with Afghanistan, a main producer of opium. This can influence opium availability to addicts and consumption of higher amounts of lead contaminated opium by patients.

Among 254 selected cases with BLL ≥ 10 µg/dl, 206 (81.1%) were anemic. We found a significant correlation between BLL and decrease in RBC counts, Hb, Hct,
MCH, as well as an increase in RDW. Sideroblastic anemias are a group of anemias characterized by an increase in iron stores and the presence of ring sideroblasts in the marrow. They are caused by various etiologies including lead toxicity (McPherson, 2017). Lead can cause anemia by interfering with some enzymes involved in the biosynthesis of heme, as well as enzymes work in maintaining RBC membrane integrity. So, it can lead to anemia by reduction in production and hemolysis (Halmo and Nappe, 2019). The Anemia of lead poisoning is mostly of normochromic normocytic and sometimes hypochromic microcytic (Gidlow, 2015). Domeneh et al. (2014) reported that 41% of their addict patients were anemic. The mean BLL of their patients was 11.75±6.06 and 7.07±3.61 for oral or inhalational users, respectively. The lower percentage of anemia in their study could be related to the lower BLLs of their patients. In line with our results, Nakhaee et al. (2019) as well as Patil et al. (2006) reported significantly higher WBC counts in their lead-exposed participants. In contrast Kianoosh et al. (2013) did not find a significant correlation between BLL and WBC or neutrophil counts. Further studies are needed to elucidate the association between lead toxicity and WBC count. The observed higher WBC counts may be related to other additives other than lead, which are sometimes included in opium.

Leukocytosis was found in 15% of patients in the current study. In addition, there was a significant positive correlation between BLL and WBC counts, as well as the percent of neutrophils in peripheral blood. In line with our study, Nakhaee et al. (2019) as well as Patil et al. (2006) reported significantly higher WBC counts in their lead-exposed participants. In contrast Kianoosh et al. (2013) did not find a significant correlation between BLL and WBC or neutrophil counts. Further studies are needed to elucidate the association between lead toxicity and WBC count. The observed higher WBC counts may be related to other additives other than lead, which are sometimes included in opium.

Lead toxicity, like other sideroblastic anemias, is associated to an increase in iron stores and serum iron as well as a decrease in TIBC. In this study, there were significant correlations between BLL and an increase in blood iron and a decrease in TIBC. Some authors report a negative correlation between BLL and serum Iron (Wibowo et al., 1977; Kim et al., 2003). Competition between lead and iron in occupying metal-binding proteins in plasma was mentioned as a possible explanation. A study on 111 smelter workers found no significant correlation between BLL, Iron and TIBC (Lilis et al., 1978). Lead can cause various effects on iron metabolism (Leikin and Eng, 1963; Carvalho et al., 1995). It mostly depends on the severity of lead toxicity. Iron deficiency was reported to be related to increased BLL (Carvalho et al., 1995). While, peoples heavily exposed to lead did not show correlations between BLL and serum iron (Lilis et al., 1978). Further studies are needed to elucidate the interrelations between lead and iron.

Lead is stored in the kidney and liver. It can result in a reduction of renal glomeruli as well as renal tubular damage (Kshirsagar et al., 2015; Buser et al., 2016; Nakhaee et al., 2019). In addition, lead can cause oxidative liver damage (Dadpour et al., 2016; Nakhaee et al., 2019). Some studies have shown a correlation between BLL and renal dysfunction (Wang et al., 2002; Alasia et al., 2010; Nakhaee et al., 2019). In contrast, others did not find such correlations (Gerhardsson et al., 1992; Balali-Mood et al., 2010; Kianoosh et al., 2013).
In line with the last mentioned studies, no significant correlation between BLL and serum BUN and creatinine were found in our research. There are conflicting data about the association between BLL and liver function tests. In a study by Nakhaee et al. (2019), although AST and ALT levels of patients were within the normal range, there was a significant correlation between BLL and serum levels of these enzymes. Bhagwat et al. (2008) and Dongre et al. (2010) reported similar results. In line with our study, Abbasi et al. (2009) found no correlation between BLL and liver function tests, including bilirubin, AST, ALT and ALK. Finding no correlation between BLL and kidney and liver function tests in the present study, may be attributed to the fact that BLL is not always a good predictor of body lead load (Gidlow, 2015). In acute and sub-acute toxicities, the BLL is much higher than chronic toxicity with the same amount of total body lead. It may explain fewer toxic effects on kidney and liver.

Conclusion

We found high number of cases with lead toxicity as well as higher levels of BLL in our center comparing the population-based and studies reported BLL in addicts in Iran. Lead causes severe damage in many organs in the body and its toxicity presents with various clinical and laboratory findings. Therefore, any patient with unexplained normo or hypochromic anemia with increased blood iron and decreased TIBC is better to be evaluated for BLL.

Conflicts of interest

The authors declare that they have no competing interests.

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