Heavy Metal Intoxication

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Although some debate exists with regards to the subject, elements which are classified under 'heavy metals' have come to be those which pose a threat to humans in terms of toxicity. Intoxication with heavy metals is not a typical diagnosis as it is fairly uncommon. This can impose a risk on people who fail to be diagnosed and removed from the source of exposure, increasing morbidity and mortality.

For the purposes of this review, Cadmium and Mercury will be discussed. A brief introduction of each element's chemical and physical properties will be given, as well as its sources in the environment and any uses. Each metal's toxicity will be illustrated using actual cases of poisoning. Any treatments for intoxication will be explained at the end of each section.

Overview on Cadmium

Cadmium (chemical symbol Cd) is a transition metal element. Although the pure metal is not typically found in nature, it is associated with zinc ores, and to a certain extent to the ores of lead and copper. For this reason, it is difficult to eliminate the by-product of Cd from the metallurgy of the aforementioned elements. Other industrial sources of Cd include smelting of other metals, combustion of fossil fuels, incineration of waste and the utilization of phosphate and sewage sludge fertilizers (Alexandar et al., 2009).

The uses of Cd in industry include the production of coatings, pigments, plastics, plastic stabilizers, batteries, photovoltaic devices and nonferrous alloys. When it is released in the environment it can contaminate the air, water and soil. Cd is released from natural mechanisms including forest fires, marine aerosol production and volcanic eruptions among other natural phenomena (Faroon et al., 2012).

Typically found in its +2 oxidation state, Cd ions exist in their hydrated forms as well as complexed to organic or inorganic substances. The more soluble forms have the ability to migrate in water, whereas insoluble forms tend to adsorb to sediments and become immobilized (Faroon et al., 2012).

According to data collected in the European Union (EU), it is estimated that 90% of Cd exposure in non-smokers occurs from food, particularly cereals and vegetable crops. Plants can take up Cd salts from the soil. This uptake depends on factors such as the type of soil, the solubility of Cd in it and the species of the plant in question. Other sources of exposure include meat and fish, although these are less significant. However, consumption of organs such as liver and kidneys from exposed animals contributes a more noteworthy source of Cd, as the element tends to accumulate in these organs. For non-smokers, air and water pose negligible threats in terms of exposure as very low levels are present (Alexandar et al., 2009).

Data collected in the United States (US) complies with the report issued by the European Food Safety Authority. Exposure to non-smokers in the US is largely from the diet, with females exhibiting a larger uptake of Cd from their gastrointestinal tract than males. The highest amounts of Cd were found in leafy vegetables such as spinach and lettuce, and in staple foods like potatoes and grains. Naturally high levels of Cd can be found in peanuts, soybeans and sunflower seeds (Faroon et al., 2012).

Smokers showed an overall high mean blood Cd compared to non-smokers. This could be measured as high as 1.58µg/L, compared to the average value for adults, 0.38µg/L. The reason for this markedly high value is the fact that tobacco leaves naturally accumulate Cd more readily than other plants. It was also noted that non-smokers exposed to second-hand smoke were also at risk for Cd accumulation (Faroon et al., 2012).

Cd biomarkers are typically detected in blood, urine, hepatic tissue, faeces, renal tissue, hair and other tissues (Faroon et al., 2012). Blood Cd levels tend to be more closely related to recent Cd exposure, whereas urine Cd levels reflect body burden over lengthy exposure, and tend to increase with renal tubular dysfunction. Liver Cd levels are also related to duration and intensity of exposure regardless of renal function (Roels et al., 1981).

Cadmium Toxicity

This metal ion can pose numerous health risks. Cd2+ does not have any known use in animal or human biology, however its divalent nature can assimilate roles performed by other essential metals. It can cross membranes using metal transporters. When it gains entry within the cell, Cd2+ can bind ligands with a particularly high affinity. Clearance is difficult, explaining the long term storage of Cd in intestinal, hepatic and renal tissues. The biological half life of this metal is estimated to vary from 10 to 30 years. Its toxicity stems from its interference with iron, calcium or zinc homeostasis, which are necessary for basic cellular functions (Alexandar et al., 2009).

The acute effects of Cadmium

Metal fume fever is a condition which develops within 48h of exposure to metal fumes and is typically caused by cadmium oxide, although other metal oxides can also cause it. Patients present with flu-like symptoms, with resolution within 24-48h of onset. The pathogenesis is not fully understood; however it is hypothesized that upregulation of protein release in response to stress occurs. An example could be heat shock proteins, which are chaperone proteins released in response to hypothermia and other environmental stresses. The advised treatment is immediate removal from the source of Cd exposure, bed rest, antipyretics and treatment for osteoporosis (Malaguarnera et al., 2013).

The chronic effects of Cadmium

Metallothioneins are sulfur-containing proteins rich in the amino acid cysteine, which typically bind metal ions in the body; with the example of haemoglobin. These chelators have numerous important functions including transport, detoxification, sequestering and metabolism of metal ions. Metallothioneins bound to Cd are reabsorbed in kidney tubules (Nordberg & Nordberg 2009). Renal cortex Cd accumulation results in tubular proteinuria with measurable loss of low molecular weight proteins. These include retinol binding protein, β-1-microglobulin and β-2-microglobulin. Progression of renal damage results in glucose, amino acids and minerals being lost in the urine. Long term exposure eventually damages the renal glomeruli and results in a drop in glomerular filtration rate. Uraemia can develop in serious cases. Reversibility of Cd-induced tubular dysfunction depends on the severity of proteinuria, which is quantified by the amount of β-2-microglobulin (B2M) in the urine (Table 1.1) (Nordberg 1998).

Itai-Itai disease (IID) is a painful disease which presents with multiple distortions and fractures of the long bones. It is the most severe form of chronic Cd poisoning by ingestion. Due to a zinc mine located upstream from Toyama Prefecture, the Jinzu River was contaminated with Cd. People who lived in the river basin showed the symptoms of Itai-Itai (Baba et al., 2014).

A study was conducted on post-menopausal women living in this area. The aim of the study was to link osteomalacia with renal tubulopathy. Two methods for cause of development of osteomalacia were considered; a direct and an indirect pathway. In the direct pathway, osteomalacia is thought to be caused by the direct interference of Cd with bone metabolism. In the indirect pathway Cd causes Fanconi syndrome, which is the damage of the renal proximal tubule resulting in loss of calcium and phosphate in the urine and the subsequent development of osteomalacia. Although the study does not entirely dismiss the direct pathway, histopathological analysis showed that osteomalacia development was linked to the Cd concentration in the renal cortex but not in bone. Figure 1.1 shows the damage caused by Cd; in comparison to the normal subjects, there is notable atrophy in the renal cortex of IID patients, as well as osteoid lesions in their bones (Baba et al., 2014).

Cd exposure by inhalation has been linked to lung cancer in studies based on men who were exposed to Cd at their workplace; however, these studies did not account for other significant factors such as the possibility of other carcinogens or the smoking habits of the subjects. Considering different studies, it was concluded that Cd was not a cause of lung cancer; rather, cigarette smoking and exposure to arsenic were to blame (Faroon et al., 2012).

Treatment for Cadmium Toxicity

Treatment of Cd exposure is largely symptomatic. Patients exposed to oral Cd salts should be given a gastric lavage or induced to vomit. Inhalation exposure treatment consists of removing the subject from exposure and giving oxygen as necessary. Chelating agents are contraindicated as they are nephrotoxic in combination with Cd (Nordberg, 1998).

In a study using a rat model, administration of Chlorella vulgaris was observed to increase excretion of Cd in the urine and faeces, as well as preventing its uptake from the gastrointestinal tract. The

B2M in urine (μg/g creatinine)	Clinical interpretation
<300	Within the reference interval.
300-1,000	Incipient cadmium tubulopathy, possibly reversible upon cessation of exposure or forerunner a) of accelerated decline of GFR; increased incidence of renal stones.
1,000-10,000	Irreversible tubular proteinuria. GFR may still be normal.
> 10,000	Overt cadmium nephropathy and usually decreased GFR.

[a] this refers to values that have been confirmed in the same subject at least twice in two repeated measurements over a six-month period.

Table 1: Levels of B2M in the urine compared with the level of damage achieved and the possibility for reversal (Nordberg 1998).

precise mechanism by which excretion is increased is unknown. Prevention of Cd uptake is thought to be due to dietary fibre found in Chlorella, which traps Cd in the intestinal epithelium. Epithelial cells are then lost in the faeces by desquamation (Shim et al., 2009).

Overview on Mercury

Mercury (chemical symbol Hg) is a transition metal which occurs in three variations; the elemental form and in inorganic and organic compounds. In its elemental form Hg is a liquid at room temperature. Depending on how high the temperature, colourless and odourless vapours are emitted (Risher & DeWoskin, 1999).

In its inorganic form, Hg occurs as salts of chloride, sulfide or oxides. A large majority are white salts, with the exception of cinnabar. Cinnabar is mercury sulfide, a red salt which converts to black following light exposure. Organic Hg compounds are also known as organomercurials. The most common organomercurial is methylmercury, a crystalline white solid. Other compounds include dimethylmercury, a colourless liquid, and phenylmercury, a white solid (Risher & DeWoskin, 1999).

In nature the commonest forms of Hg are elemental, mercuric chloride, cinnabar ore and methylmercury. Liquid elemental Hg has multiple uses, such as the production of caustic soda, gaseous chlorine, as well as the extraction of gold from it ore or gold-containing items. Elemental Hg is used in measuring devices like thermometers and barometers, and also batteries and electric switches. Inorganic Hg is used in fungicides, skin-lightening creams, paints, tattoo dyes, topical antiseptics as well as disinfecting agents. Prior to 1991, organic Hg compounds were used in antifungal agents, but this use was discontinued after it became known that Hg vapours were released from these products (Risher & DeWoskin, 1999).

Hg constitutes about 50% of the components of dental amalgam. Other metals include silver, copper, tin and trace metals. Dental amalgam is used to treat dental cavities. Its continued use till today is mainly due to its quality and the fact that most dentists are trained to use it, as opposed to other modern substitutes. These fillings leach Hg when they are being inserted, removed, as they deteriorate with time and from the buried or cremated remains of people who had these fillings. According to the final report prepared for the European commission, the phasing out of Hg-containing dental amalgam would be difficult for a number of reasons, including the expense of dental amalgams that do not contain Hg. Also, dentists would require training to insert these amalgams as well as new equipment with it. Health services in the EU do not always cover these costs; dental fillings are not covered by the national health insurance schemes in Malta (Mudgal et al., 2012).

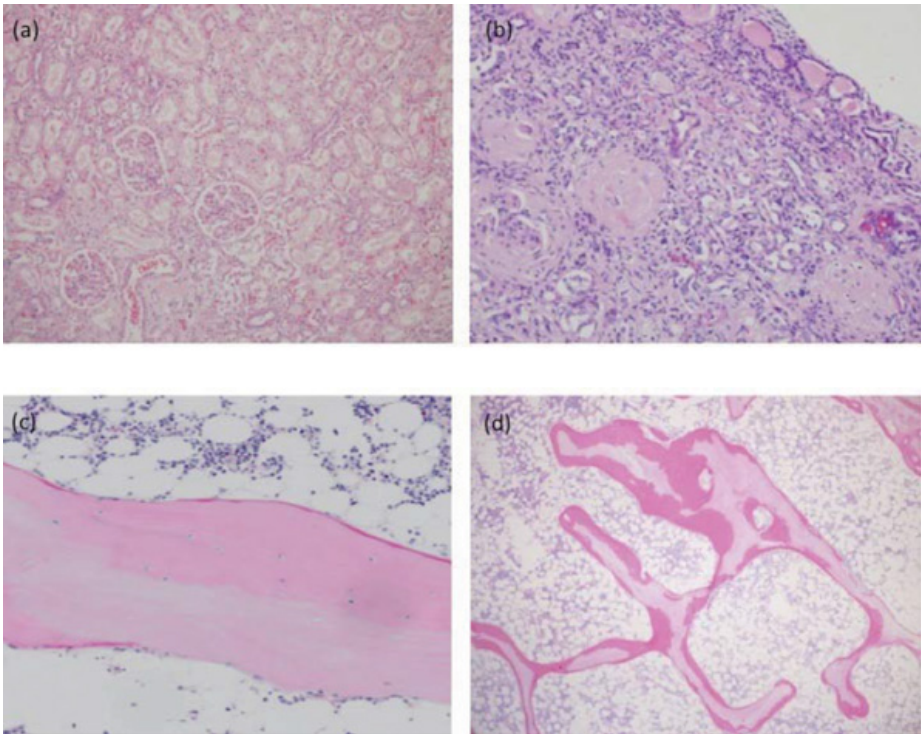

Figure 1: Histological sections of normal renal cortex (a), IID patient renal cortex (b), normal iliac bone (c) and IID patient iliac bone (d). Renal cortex atrophy in (b) and iliac bone osteoid lesions in (d) can be observed following prolonged exposure to Cd (Baba et al., 2014).

Mercury Toxicity

Hg poisoning in the clinical setting is largely due to suicide attempts by ingestion of mercury cyanide or other compounds. Accidental poisoning is unusual, although reports of Hg exposure by youngsters from broken mercury thermometers and barometers have been reported. Inorganic Hg compounds in their pure powder form are the cause of non-fatal poisoning in adults (Triunfante et al., 2009).

Chronic exposure of methylmercury from bioaccumulation in fish is a cause of concern (Triunfante et al., 2009). Hg in trace amounts dissolves in water and is converted into toxic methylmercury, which is absorbed by fish through the gills and by consuming smaller aquatic organisms contaminated by Hg. Larger fish carry the largest amounts of Hg due to predation. A study conducted in Ghana analysed the content of heavy metals including Hg in several canned fish products. Canned tuna brands showed the highest Hg levels from the fish analysed (Okyere et al., 2015).

Intoxication from inhalation of metallic Hg vapour typically results in respiratory distress, which can result in death if severe (Triunfante et al., 2009). When Hg is inhaled, 74-80% of the dose is absorbed via the alveolar membrane in the lungs. It is then transported to a number of tissues including the liver, central nervous system and especially the kidneys. In a case report by Gul Oz et al. (2012), a family of four suffered varying

degrees of Hg poisoning after one of the children brought home a minute piece of Hg in a glass from school, which broke and was vacuumed up by the mother in a non-aerated room.

Nephrotic syndrome due to Hg intoxication developed in the mother following 3 months from exposure. Kidney malfunctions present with proteinuria, which can be for one of two reasons: antigen-antibody complexes that form as a result of excess Hg are not effectively cleared and result in damage to the glomeruli (Figure 2.1); alternatively Hg ions cause direct damage in renal tubules (Gul Oz et al., 2012).

The initial effects of Hg poisoning are flu-like symptoms within 1 to 3 days of exposure. These effects include excess salivation, oedematous gingiva, fever, dry cough, diarrhoea, nausea and vomiting. Later effects include non-cardiogenic pulmonary oedema as well as pneumothorax. In post-mortem analyses of Hg-exposed lungs, damage such as intense corrosion of the bronchiolar epithelium and necrotizing bronchiolitis with fluid accumulation in the alveoli and the interstitium. Dysfunctions in other systems such as the kidneys, liver, blood and skin have also been reported (Gul Oz et al., 2012).

The final phase of Hg poisoning is typically a progressing hypoxic state which can lead to death. If the patient survives the intoxication, there may be residual damage in the form of gingivostomatitis, tremors as well as erethrism, which can manifest as loss of memory, emotional instability, insomnia, depression and shyness (Gul Oz et al., 2012).

Injection of metallic Hg with the intent of suicide is also reported. Intravenous injection leads to pulmonary embolization by globules of Hg, and patients present with chest pain, dyspnoea, fever and cough. Other signs include changes in the patient's electrocardiogram, impairment of renal function and dermatological symptoms. Subcutaneous Hg injections results in inflammation that is localised, granulation tissue and the formation of abscesses. Eventual systemic involvement is also expected (Alhamad et al., 2012).

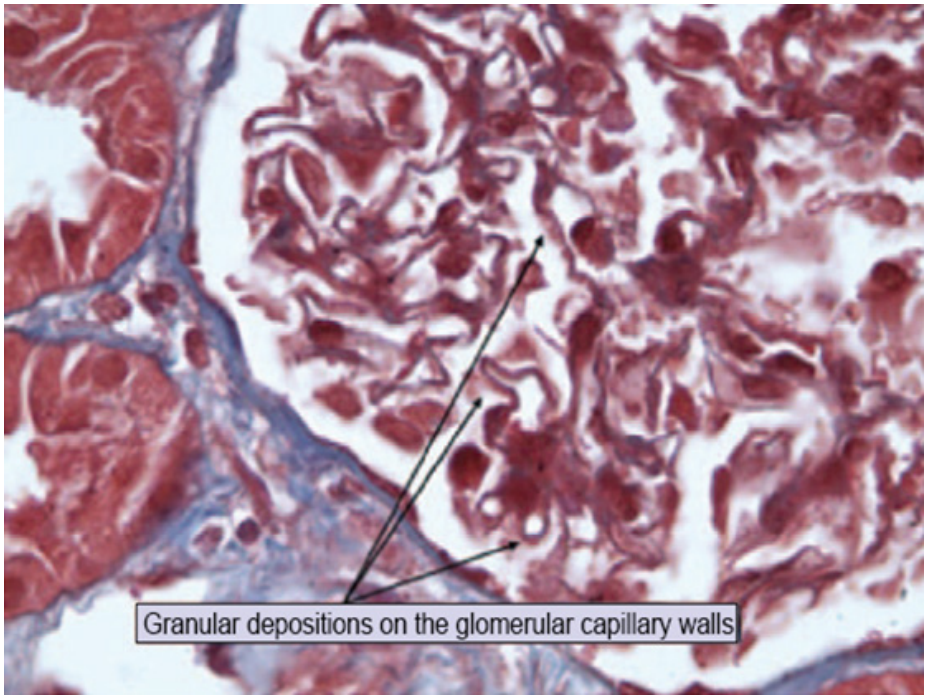

Figure 2: Histological section showing depositions on the capillary walls of glomeruli made up of granules formed by antibody-antigen complexes that did not clear successfully, (Gul Oz et al., 2012).

Treatment for Mercury intoxication

British Anti-Lewisite, also known as BAL, was developed in warfare as an antidote to lewisite, which is an arsenical vesicant. BAL's chemical name is 2,3-dimercaptopropanal, and it is an oil which is freely absorbed by the skin. It binds lewisite to form a stable compound, therefore removing this toxin's effect on the enzyme pyruvate. BAL can also prevent the vesicant effects of lewisite if applied before exposure, but can reverse the initial symptoms up to two hours after exposure. The resulting compound is then excreted in the urine. This drug was also used to treat Hg poisoning. (Peters 1949).

In rats, intravenous BAL proved effective in preventing the acute systemic poisoning caused by mercury chloride. When BAL was supplied by injection as well as oral dosage, it also safeguarded the rats from fatal doses (Stocken 1946).

In the 1950s, chemically similar dithiols which could also dissolve in water were produced; unithiol (DMPS) and succimer (DMSA). Treatment with these substances is required as early as possible following Hg exposure, as their as their effectiveness decreases with time. In chronic intoxication, DMPA and DMSA chelation appears to reduce the inorganic Hg burden on some organs. However, in morbidity and mortality terms, the benefit has not yet been concluded. Some observed side effects of DMPS and DMSA include allergic reactions with widespread rashes in 1 to 10% of subjects in certain studies. Other effects include gastrointestinal issues and reversible rises in hepatic transaminases and drops in white blood cell count (Kosnett 2013).

Conclusion

Diagnosis of heavy metal intoxication is not one of the first which comes to mind when presented with a case, and therefore achieving a good standard of care requires understanding the sources of exposure of each metal as well as the pathophysiology of poisoning. This is also true from the point of view of researchers looking for possible prevention treatments.

Exposure can occur from medication, diet, the environment and on the workplace. For this reason, a thorough history of possible heavy metal intoxication cases should be gathered and scrutinized

before any attempt at a diagnosis is made. When multiple patients present with similar symptoms, it can be advisable to further investigate any linking factors. The possibility of intentional poisoning as a means of suicide or murder cannot be excluded.

The primary treatment is removing the patient from the source of exposure as soon as possible. Further follow-up depends on the type of metal poisoning; chelating agents discussed in the essay are used at the discretion of the physician in charge, due to side effects and the chance of nephrotoxicity especially when the kidneys have already been implicated.

Future research should be based on the prevention as well as treatment. New and better chelators are a good avenue, however other studies have focused on substances like Vitamin E and NAC, as well as organisms like Chlorella vulgaris for preventing the toxic effects of specific metals when administered concomitantly. More studies would be required before any conclusions can be reached; however, current studies are showing promise.

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