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Mercury vapor inhalation and poisoning of a family

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Abstract
Acute mercury vapor poisoning is a rare but fatal toxicological emergency. People are exposed to mercury in daily life by the way of foods, vaccines, antiseptics, ointments, amalgam or occupation. We present here, the clinical picture and management of four members of the same family who were exposed to elemental mercury. Three of the family members were seen in another hospital with malaise, fever, erytematous rash and pulmonary problems. Their questioning revealed the mercury exposure. Having a suspicion of heavy metal intoxication, blood and urine mercury levels were measured and mercury intoxication was diagnosed. On admission to our hospital, two patients already had chelation therapy. In three of them we found three distinct abnormalities: encephalopathy, nephrotic syndrome and polyneuropathy. The fourth family member had minor symptoms. This family is an example for the inhalation exposure resulting from inappropriate handling of liquid mercury. During the first days, flu like illness ensues. Then, severe pulmonary, neurological, renal, hepatic, hematological and dermatological dysfunctions develop. Blood and urine mercury levels should be tested on suspicion, but it must be kept in mind that blood level is unreliable in predicting the severity of mercury toxicity. The priority in the treatment should be removing the patient from the source of exposure. Then British anti-Lewisite, edetate calcium disodium, penicillamine, Sodium 2,3-dimercaptopropane-1-sulphonate and 2,3-dimercaptosuccinic acid can be used for binding the mercury. We conclude that since mercury-containing devices are present in daily life, physicians must be able to recognize the clinical manifestations and treatment of mercury poisoning.

Keywords: Acute intoxication, chelation therapy, inhalation exposure, mercury

Introduction
Mercury is a naturally existing heavy metal. People are frequently exposed to mercury in daily life by the way of foods, vaccines, antiseptics, ointments and amalgam or because of their occupation. Mercury is present in three forms: elemental, organic and inorganic compounds. Elemental form enters the body especially through inhalation, distributes thoroughly and is deposited in every organ and tissue. Major sites of this distribution and deposition are nervous, cardiovascular and immune systems, kidneys and skin. Mercury is silver like shiny liquid metal, but it can vaporize at room temperature and the resulting odorless and tasteless mercury vapor is very toxic.

We present here the clinical picture and management of four members of the same family who were exposed to elemental mercury.

Case 1
A 42-year-old female without any previous medical problem presented with fever, malaise, flushing over her face and hands and loss of appetite. Before the development of these symptoms, one of her children had brought home a piece of peanut sized mercury in a glass from the school chemistry laboratory. While the children were playing with it, the glass fell down and the mercury spilled over the floor of the living room. She tried to gather the spilled mercury and vacuumed it two consequent days but didn’t air the room. On the third day of exposure, cough and malaise began and three days later she was admitted to a local hospital for the aggravation of these symptoms along with dyspnea, fever (41.5°C) and erytematous macular eruptions. A detailed questioning revealed her mercury exposure for 6 days. She received intravenous (iv)
Sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) treatment for seven days: first day 2400 mg, second day 1600 and 600 mg on the following days. On the first day of the treatment, fever and rash disappeared. On the 18th day of the treatment, she developed petechiae and thrombocytopenia (plt: 13,000). A bone marrow aspiration was performed with the prediagnosis of immune thrombocytopenic purpura (ITP) and showed hypocellularity. Despite the hypocellular marrow, a diagnosis of ITP was entertained and fluocortolone 60 mg/day was started – the platelet count was 100,000/mm³ in the third month. In the second month of mercury exposure, 24-h urine mercury level was 55 µg/L (0.1–20 µg/L). Her urine analysis showed (+++) proteinuria and the patient experienced periorbital, palmar, lower extremity edema which were treated with furosemide and ramipril.

She was admitted to our hospital in the third month of her mercury exposure with malaise, sore throat, lumbar and lower extremity pain and excessive hair loss. The physical examination revealed high blood pressure of 140/100 mmHg, diffuse edema, hyperemia of hands and feet. Her laboratory findings showed a hemoglobin level of 16.5 g/dL, erythrocyte sedimentation rate of 52 mm/h; her total cholesterol level was 701 mg/dL, LDL-cholesterol 531 mg/dL, triglyceride 473 mg/dL, albumin 1.93 g/L, 24-h urine mercury level 73 µg/L (0.1–20 µg/L) and serum mercury level 54 µg/L (0.6–59 µg/L). With the diagnosis of nephrotic syndrome a renal biopsy was performed which showed numerous inflammatory cells in the glomerular capillary lumen and interstitial edema. No tubulointerstitial damage were noted, the vessels were normal and the global diffuse IgG containing immune-complex deposition over the glomerular capillary endothelium was consistent with membranous glomerulopathy (early stage). There was no finding of glomerular sclerosis, interstitial fibrosis and tubular atrophy (Figures 1 and 2). Complement 3 and 4 levels were normal, antinuclear and anti-DNA antibodies were negative and urinary protein loss was 9.7 g/day (Figure 3).

At the beginning, a chelation therapy with iv DMPS 5–10 mg/kg/day was started. Upon the diagnosis on the tenth day, 2,3-dimercaptosuccinic acid (DMSA) 200 mg/day iv was added and continued for 12 days. She also received prednisolone, angiotensin-converting enzyme inhibitor (ACEI) followed by angiotensin II receptor blocker (ARB), atorvastatin, furosemide and spironolactone which improved her edema, proteinuria and hypalbuminemia. Her blood pressure returned to normal level with the loss of 20 kg of her body weight. She was given tramadol and gabapentin for her lumbalgia and limb pain. She was also diagnosed to have hypothyroidism and treated with L-thyroxin. Her electromyography (EMG) and the thyroid imaging were normal. An abdominal ultrasonography revealed hepatomegaly, increased echogenicity of the liver parenchyma and normal kidney size. The second course of chelation with iv DMPS 200 mg/day and DMSA 200 mg/day lasted for 5 days. The proteinuria lasted for 2 years.

Case 2
Nineteen-year-old male patient who was the son of case 1 was admitted to the same local hospital along with his mother for having malaise, cough, fever (41°C) and disseminated erythematous rash. He was treated with a diagnosis of pneumonia, but had no response. Then, the exposure of the family members to mercury vapor was determined and his blood and 24-h urine mercury levels were found to be high. With an iv chelation therapy of DMPS for 12 days, his body temperature dropped to normal levels. A month later, he experienced muscle pains and jerks on his arms, legs and perioral zone. The 24-h urine and blood mercury levels were 50 µg/L (0.1–20 µg/L) and 32 µg/L (0.6–59 µg/L), respectively, in the second month of the exposure. The patient’s complete blood

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count, renal and hepatic function tests as well as his EMG were normal. This time DMPS treatment was given iv for 5 days and he was referred to our hospital.

He was in the third month of mercury exposure when admitted to our hospital with malaise, loss of appetite and weight (15 kg in 3 months), generalized muscle pain, peri-articular low extremity pain, constipation, periodic chest pain that caused dyspnea, dry mouth, polyuria, polydipsia, hyperhidrosis, photophobia, insomnia and hair loss. The physical examination revealed hypertension (140–155/80–100 mmHg); tachycardia (108/min); hyperemia on the dorsum of his hand; paleness of the hands and feet; reddish macular eruptions on his sternum, lateral parts of his feet and upper part of his back. He had bilateral posterior cervical lymphadenopathy and was fully conscious. Neurological examination revealed motor deficit in the proximal muscles of the lower extremities and twitching of proximal muscles of both extremities which aggrivated by tapping. No sensory deficit was present, cerebellar tests were normal. The laboratory evaluations showed normal complete blood count. Renal, hepatic and thyroid function tests as well as renal arterial Doppler ultrasonography were all normal except moderate proteinuria (24-h urine protein loss was 871 mg/day); 24-h urinary mercury level was 15 μg/L (0.1–20 μg/L), and blood mercury level was 34 μg/L (0.6–59 μg/L). Intravenous chelation therapy was started with DMPS 200 mg tid (400 mg/m²) and DMSA 400 mg/day (300 mg/m²) for 5 days and continued for 12 days with the doses of DMPS 200 mg bid and DMSA 400 mg/day. At the end of the treatment 24-h urinary mercury level was 6.9 μg/L.

During follow-up, a beta blocker and ACEI were added to the therapy for the ongoing tachycardia, hypertension and proteinuria. After chelation treatment tachycardia regressed, his blood pressure dropped to 100–10/60–80 mmHg. The echocardiography showed the impairment of the left ventricle and hypokinesia of the midinferior basal wall of the heart with an ejection fraction of % 68. His coronary computed tomography angiography was normal. The heart rate variability test proved that the heart was diffusely affected in both sympathetic and parasympathetic directions. After finishing the chelation procedures photophobia, insomnia and hypertension disappeared. An EMG showed fasciculations and myokymic discharges in all the muscles, especially in the lower extremities. There was no sign of polymeuroopathy and the involvement of the peripheral nervous system was the cause of these myokymic discharges. His extremity pain was stabilized with pregabalin and fentanyl transdermal patches. Four months later, his echocardiography was completely normal. The pain decreased in the fifth month and continued only in the right hand and foot. The twitching lessened but continued. The hair loss, malaise and loss of appetite completely disappeared. The pain disappeared and pregabalin was stopped at the first year.

**Case 3**

Twenty-year-old male patient, the other son of case 1 and the brother of case 2 presented with malaise, fever and rash. He was hospitalized in the same local hospital and treated with a suspicion of avian influenza. However, in the following month after discharge patient noticed progressive low extremity weakness, pain and tinnitus. He was also experiencing nausea, vertigo, dysarthria, tremor and hallucinations and had difficulty in walking. He lost 6 kg in 1 month. After obtaining a history of
mercury vapor exposure, he was further tested. The blood and 24-h urinary mercury levels were 39 and 202 µg/L respectively. EMG evaluation showed demyelinating neuropathy. With the diagnosis of mercury intoxication (parenteral) DMPS treatment was started, but his symptoms further progressed and the patient was transferred to our hospital.

On admission, the patient was somnolent, had tachycardia and hypotension. Physical examination revealed hepatomegaly, rash over the trunk and inguinal area and palmar hypoesthesia. Tachycardia was attributed to autonomic dysfunction which associated the mercury intoxication. His echocardiography was normal. Blood and 24-h urinary mercury levels were 25 and 45 µg/L respectively. Intravenous DMPS 200 mg bid treatment was started. On the ninth day of his admission he was intubated due to hypoxemia. As he was having hypo and hypertensive episodes, a jugular catheter was implanted and sometimes a vasopressor was indispensable. Due to his 2.5 g/day proteinuria ACEI and spironolactone treatment was applied. During the follow-up deep venous thrombosis developed. He was anticoagulated and a treatment was applied. During the follow-up days DMPS treatment was delayed. However, he finally received the treatment efficiently. The symptoms regressed and disappeared with parenteral DMPS treatment and mercury levels decreased progressively.

**Case 4**

Forty-nine-year-old male, the father of the family, was evaluated after family members presented with mercury intoxication. In the initial evaluation he had excessive sweating, myalgia and had a urinary mercury level of 12 µL. He was observed without any medical therapy and he is still under follow-up without clinical symptoms.

**Discussion**

In recent years, elemental mercury has proven to be a potential source of intoxication through either unintentional exposure or exposure resulting from inappropriate handling of liquid mercury obtained from school science laboratories, abandoned industrial facilities, or warehouses (Orloff et al., 1997; Nickle, 1999; Risher et al., 2003). By the way of inhalation, 74–80% of the inhaled dose of mercury is absorbed through alveolar membrane (Hursch et al., 1976; Risher & Dewoskin, 1999; Risher et al., 2003; Gattineni et al., 2007). After the absorption, it is transported to several tissues, especially central nervous system, kidneys and liver. The kidney is the major site of deposition for mercury derived from inhalation exposure to mercury vapor. The severity of the clinical presentation depends on the length and amount of the exposure.

The family in this report is a perfect example for the exposure resulting from inappropriate handling of liquid mercury which was obtained from a school science laboratory. One of the family’s children had brought a piece of mercury from school to home. While the children were playing with it in their living room, it fell down and spilled over. The mother tried to gather the spilled mercury and vacuumed it, but didn’t air the room. Two days later, she noticed that there were still mercury particles on the floor and vacuumed again. Since the mercury spilled over in the living room, the family members who spent more time in this room were severely affected.

Mercury vapor intoxication is discussed under three phases (Ellenhorn et al., 1997; Lim et al., 1998). In the initial phase, during the 1–3 days of exposure, flu like illness ensues. Hypersalivation, swollen gingiva, dry cough, dyspnea, fever, abdominal pain, nausea, vomiting, and diarrhea may develop within a few hours after exposure (Matthes et al., 1958; Snodgrass et al., 1981; Lilis et al., 1985; Levin et al., 1988). In our first three cases, we observed flu like illness during the first week of the mercury exposure.

In the intermediate phase, multisystem findings especially severe pulmonary toxicity is noted. In this phase noncardiogenic pulmonary edema, bronchiolitis, pneumonia, pneumonitisinum and pneumothorax were reported (Snodgrass et al., 1981; Lilis et al., 1985; Rowens et al., 1991). Postmortem analyses of lungs exposed to mercury vapor have shown severe erosions of the bronchial epithelium, necrotizing bronchiolitis with alveolar and interstitial fluid accumulation (Campbell, 1948; Tennant et al., 1961; Solis et al., 2000). Renal, hepatic, hematological and dermatological dysfunctions may be seen. In case 1, thrombocytopenia was observed in the beginning. There are a few reports in the literature defining an association between elemental mercury toxicity and thrombocytopenia (WHO/IPCS, 2003). We did not figure out whether that was due to the intoxication or the adverse effect of the drugs. Nevertheless, this condition recovered following chelation treatment. In the third month of the exposure, nephrotic syndrome developed in the same case with all the pathologic features which were compatible with mercury intoxication. Nephrotoxicity presents mainly with proteinuria either from glomerular damage due to idiosyncratic immune-complex glomerulonephritis or from tubulopathy resulting from direct damage of renal tubules by mercury ions (Ellenhorn et al., 1997; Koyun et al., 2004). The use of mercurial diuretics or other forms of mercury exposure may result in nephrotic syndrome with varying pathologic features. The biopsies of most cases revealed membranous nephropathy (Friberg et al., 1953; Williams & Bridge, 1958; Becker et al., 1962; Oliveira et al., 1987). Protein excretion rates as high as 44 g/day have been reported (Cameron & Trounce, 1965). In a number of cases, such as the young women in Kenya who used mercury-containing skin lightening cream, minimal renal changes rather than membranous nephropathy were reported (Barr et al., 1972). Nephrotic syndrome may also occur in association with occupational exposure to mercury (Friberg et al., 1953; Kazantzis et al., 1962; Agner
A high degree of exposure. The obvious and most important consideration should be considered if there has been renal toxicity due to mercury. However, the administration of chelators should be considered if there has been a high degree of exposure, but it may take several months (Friberg et al., 1953; World Health Organization, 1991; Kazantzis et al., 1962). In our case 1, relatively rapid beginning of renal damage and regression with chelation was noted. This clinical progress is consistent with the renal dysfunction related to mercury intoxication. After the chelation therapy, proteinuria decreased and albumin levels increased. In follow-up, she was given an ACEI/ARB, her proteinuria decreased incrementally and disappeared in the second year. In case 2, we still observe moderate proteinuria.

In the last phase, mortality is generally experienced with progressive hypoxia. If the patient survives, gingivostomatitis, tremors and erethism (memory loss, emotional lability, depression, insomnia and shyness) can be observed (Solis et al., 2000). Case 3 had severe encephalopathy on admission. He became hypoxic and was intubated after hospitalization. With chelation therapy, his clinical findings improved and he was extubated. Our patent has loss of memory for this period of time.

In various case series, especially exposure to methyl mercury was showed to cause cardiovascular problems (Guallar et al., 2002; Yoshizawa et al., 2002; Bolger & Schwartz, 2002). In our first three cases, who had severe intoxication, symptoms related to cardiovascular system (hypertension, tachycardia, decreased autonomic modulation of heart rate, arrhythmia) were detected. Mercury intoxication should be differentiated from pheochromocytoma since tachycardia and hypertension is also a characteristic of this disorder. In inorganic mercury poisoning, the metal combines with the sulfhydryl group of S-adenosylmethionine, which acts as a cofactor for catecholamine-O-methyltransferase (COMT). COMT inhibition leads to the accumulation of catecholamines, typically noradrenaline, adrenaline and dopamine and to a lesser degree vanyl mandelic acid (Henningsson et al., 1993; Baudouin et al., 1997). This catecholamine excess is responsible for the pheochromocytoma-like syndrome which explains the hemodynamic symptoms of acrodynia. Acrodynia is a form of mercury poisoning in which the clinical signs include mental changes (insomnia and irritability), pain in the extremities, typical skin lesions (swelling and irritation of palms and feet followed by skin desquamation), profuse sweating, photophobia, fever and anorexia as well as hypertension and tachycardia (Wössmann et al., 1999). The majority of the affected individuals are young children. The symptoms of our cases 2 and 3 are consistent with acrodynia, but unfortunately we could not measure their epinephrine and norepinephrine levels due to technical difficulties. Although acrodynia is generally faced in inorganic mercury exposure, there are some cases showing that it can be seen in elemental mercury intoxication as we experienced in our cases (Baudouin et al., 1997; Torres et al., 2000). Thus, during the evaluation of the patients presenting with unexplained tachycardia, hypertension, mood changes, weight loss and painful extremities mercury intoxication must be considered in the differential diagnosis.

Mercury exposure may induce severe axonal sensorimotor polyneuropathy which mostly affects the lower extremities, as seen in case 2, and neurological deficits may persist in severe cases (Chu et al., 1998; Pelcová et al., 2002; Koyun et al., 2004). In some severe mercury intoxication events with pronounced neurological and nephrotic manifestations or changes in behavior and a deterioration in general status, termination of the exposure and/or administration of the chelator agents do not always lead to total recovery (Pelcová et al., 2002).

When mercury poisoning is suspected, blood and urine mercury levels should be tested. A high blood mercury level is a good indicator of acute intoxication, but in cases of acute metallic mercury poisoning, blood analysis is considered useful only when samples are taken within a few days after exposure, since mercury has a short half-life in blood (Risher & Amler, 2005). The adults who are not exposed to mercury have a blood mercury level less than 2 µg/dL (Agner & Jans, 1978). Symptoms of toxicity generally occur in individuals with blood mercury level over 5 µg/dL. In adults who are not exposed to mercury, urine mercury excretion is less than 50 µg/L in 24 h and a spot urine mercury level is less than 10 µg/L (Solis et al., 2000). In our first three cases, the severity and duration of symptoms and multisystem manifestations seemed to be out of proportion to urinary and blood mercury levels. However, because of the redistribution, blood mercury level is unreliable in predicting the severity of toxicity (Haddad et al., 1998). In some case reports, no correlation between clinical toxicity and blood and urine mercury levels is demonstrated, because mercury might be present in higher concentration in different organs (Orloff et al., 1997; Ozuh, 2000).

The first consideration in treatment should be removing the patient from the source of exposure. In some cases, symptom-based supportive treatment may be appropriate whereas high urine or blood mercury levels and more profound symptoms such as respiratory distress or acrodynia might warrant consideration of chelation (Risher & Amler, 2005). British anti-Lewisite (BAL), edetate calcium disodium, D-penicillamine, N-acetyl-D L-penicillamine and newer agents such as DMPS and DMSA can be used in toxicity for the purpose of binding the mercury and increase its excretion. DMPS has been found by a number of investigators more potent than DMSA and both DMPS and DMSA are safer than BAL or Penicillamine (Bernhoff, 2012). The efficacy of chelation therapy should be monitored by repeated clinical assessment and measurement of blood and urine mercury levels. In the condition of our cases, all the family members were removed from the house and the contaminated carpet, the source of exposure, was removed completely.
After the diagnosis and a short treatment period in the local hospital, all the family members were referred to our medical center where three of them – mother and two sons – were managed in the same internal medicine ward and the father was treated as an outpatient.

Conclusions

For clinicians, the diagnosis of mercury intoxication is challenging. The intoxication conditions present with different clinical pictures, vary from one patient to another. Similar symptoms can also be seen in some neurological problems, as side effects of some drugs, vitamin or mineral deficiency states and pheochromocytoma.

Since mercury-containing devices are present in daily life, physicians must be able to recognize the clinical manifestations and understand the importance of biological markers in making a definitive diagnosis of mercury poisoning. In addition, primary care physicians as well as critical care specialists should have knowledge on chelation therapy and follow-up of mercury poisoning.

The mercury-containing devices should be avoided in school and home. If it spreads accidentally, it must be eliminated as soon as possible. Brooms and vacuum cleaners should not be used to clean up elemental mercury. A contaminated carpet or rug should be vacuumed only with a specialized industrial mercury vacuum or be removed completely. Patients with dermal exposures should remove all the mercury-containing jewelry and wash the affected area with mild soap and water (Caravati et al., 2008). Parents and school directors should have knowledge about this subject.

In some cases of mercury intoxication, a single course of chelation therapy may not be adequate, so that symptoms and urinary mercury level of the patient must be monitored, and if necessary the chelation therapy must be repeated for several times.

Declaration of interest

The authors declare no conflicts of interest.

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