Mercury neuropathy

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Originally released November 1, 1999; last updated November 7, 2017; expires November 7, 2020

Introduction

This article includes discussion of mercury neuropathy, metallic mercury intoxication, elemental mercury, inorganic mercury poisoning, and organic mercury compounds. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Mercury neuropathy is a recognized sequela of occupational or environmental exposure to one of the various forms of the heavy metal. In this article, the author discusses common exposure sources, biological exposure indices, and clinical manifestations of mercury toxicity while focusing on mercury neuropathy for elemental, inorganic, and organic mercury. The author has updated this article to reflect the current literature regarding peripheral nervous system disease and this commonly encountered metal.

Key points

• Peripheral neuropathy from mercury exposure most commonly involves distal latency sensory slowing for short-term exposures, followed by motor slowing for more long-term exposures.
• Inorganic and elemental mercury exposures are more likely to cause peripheral nervous system complaints and findings.
• Central nervous system effects are more common with organic mercury exposures.
• Twenty-four hour urine mercury best assess exposures to inorganic or elemental mercury. Blood mercury is most appropriate for short-term exposures.

Historical note and terminology

Inorganic mercury is historically associated with environmental epidemics in Iraq and Japan, illness in occupational settings, and bizarre poisonings that have led to detective investigations.

Mercury has been known to cause illness in artists, gilders, gold refiners, and workers using metals in dyes, cosmetics, and unguents since Roman times. Later, occupational hazards of mining metallic mercury were associated with a slow death. Mercury and its salts were used as salves for syphilitics until the mid-20th century. Teething powders and antihelminthics are now rarely made with mercury (Torres 2000; Weinstein 2003).

Today, dental amalgams, eye ointments, dermatological antiseptics, and hemorrhoidal sclerotics are still common medical sources of mercury. Calomel, a type of inorganic mercury salt also known as "sweet mercury," was used in laxatives and teething powders, the latter leading to outbreaks of "pink disease" or acrodynia, a hypersensitivity syndrome to elemental mercury that can occur in children (Weinstein 2003; Khodashenas et al 2015). Occasional cases are still reported today.

Mercury is extracted from ore called cinnabar (HgS) by a roasting process. Elemental mercury, also called quicksilver or liquid silver, is a liquid at room temperature. Mercury exists in 3 oxidative states and also forms univalent (mercurous) and bivalent (mercuric) compounds. Mercuric chloride is readily dissolved, ionized, and absorbed and is more toxic than the less soluble mercurous chloride. Phenyllic mercury compounds are less toxic than alkyl mercury compounds. Toxicity of these and other organic compounds have only been recognized in this century.

Elemental mercury is used in barometers, thermometers, and gauges. Mercuric salts are used in gold, silver, and...
bronze plating processes. Mercury is also found in electronic equipment, such as batteries, switches, rectifiers, compact fluorescent light bulbs, and mercury vapor lamps. Inorganic mercury is used in photography, antiseptics, tanning processes, embalming, felt manufacturing, and wood preservation methods.

Mercury poisoning in hat makers resulted from prolonged exposure to mercury vapors in poorly ventilated factories. Lewis Carroll's Mad Hatter from the children's tale Alice in Wonderland is literature's most famous victim of mercury toxicity. A ban in the United States on the use of mercurous nitrate in the hat making industry was finally instituted in 1941.

Exposure to elemental mercury vapor occurs in the chloralkali industry during the manufacturing of chlorine. Natural gas from certain sites has been reported to contain elemental mercury, and this exposure can occur in inspectors and maintenance or equipment workers at these sites. Metallic mercury is used in dental amalgams. There has been literature discussing this as a possible low-level hazard in the dental workplace. In 1994, the Agency for Toxic Substances and Disease Registry (ATSDR) estimated 70,000 workers were exposed to mercury in the United States; 10% to 20% were estimated to experience intoxication. Some mercurichromes have been used as preservatives and antibacterials; thimerosal, which contains less than 2% mercury, has been suspected but not proven to affect autism rates.

**Clinical manifestations**

**Presentation and course**

*Environmental sources.* Because mercury is ubiquitous, exposure to mercury does not necessarily lead to illness. Mercury is present in water, air, and soil. The United States Environmental Protection Agency (EPA) has listed safe levels of mercury for humans in air, soil, and water.

The general population may experience exposure from dental amalgams or seafood. ATSDR has reported that very small mercury exposures are not necessarily harmful to one's health, but active research is ongoing. Sensitive populations are identified as pregnant woman, children under 6 years of age, those with impaired renal function, and those with hypersensitive immune systems. ATSDR has also reported that chelation and removal of amalgams is not indicated in those without health effects from mercury.

Exposures may also be experienced by religious groups who use mercurial agents in ceremonies. Exposure may occur to those using the agent as well as those who might inhale contaminated air nearby. Metallic mercury is sold in botanicas under the name azogue and is common in the Haitian and Hispanic communities. Inorganic mercury was found to be a component of a previously unrecognized source of exposure: skin care products in New York City (McKelvey et al 2011). These products were found to be produced mainly in the Dominican Republic. A large study assessing urine mercury in 1840 adults in New York City was accomplished, and it uncovered 13 individuals with levels exceeding the New York State reportable level of 20 ug/L. All of these individuals were either Hispanic or African American and between the ages of 21 and 51. Ten of these women were born in the Dominican Republic. Whitening skin creams were confiscated, tested, and found to contain 0.62% mercury by weight. Blood mercury levels were assessed and found to be positively associated with elevated urine mercury. Seventeen different products were seized from stores and tested for mercury. Eight of these were skin-lightening or beauty creams; 9 were made in the Dominican Republic and 7 listed mercury as a component of the cream.

A report from Taiwanese literature identified a 51-year-old male who was dispensed traditional medicine to treat a perianal fistula (Wu et al 2013). After using hong-dan, he presented with perianal gangrene, fever, rash, and numbness, and later he presented with progressive weakness. EMG/NCV did in fact reveal a mixed axonal along with demyelinating features (reduced sensory amplitude, prolonged F waves). Hypokalemia and normocytic anemia and elevated CRP were noted. AIDP was suspected, and despite plasmapheresis, his numbness and weakness worsened. A chelating agent, succimer (DMSA), was given, and high urine mercury and arsenic resulted. On day 27, the mixed axonal and demyelinating picture remained. Four years later, the patient had partial resolution of his symptoms, but NCV revealed nonresponse for peroneal motor and sural sensory studies. The authors wrote that hong-dan and tung oil are preparations banned due to lead content, but the paste remains compounded with unlicensed practitioners and may also contain significant mercury and arsenic.

A 4-year-old boy admitted to the hospital for rapidly progressing difficulty in walking had been treated for about 2
months with primarily ammoniated mercury ointment for itchy, macular lesions thought to be insect bites over his scalp and body. On examination, he was irritable but with an unremarkable physical examination. He did have pronounced weakness of the flexors of the feet and less of the legs, and his muscles of the upper extremities were slightly weak but no atrophies or fasciculations. It was noted that he had no signs of acrodynia; however, with his irritability, polyneuropathy, albuminocytologic dissociation in the CSF, 9% eosinophils of the peripheral blood, and history of prolonged use of ammoniated mercury ointment, mercury intoxication was suspected. This was confirmed by 24-hour urine mercury level of 0.3 mg/L. Patient was treated with dimercaprol (BAL) 3 mg per kg body weight 4 times a day, then twice daily. The patient did show progressive improvement in strength, and when re-examined as an outpatient a year later, he walked normally and demonstrated no motor weakness. Achilles reflexes, however, were still absent. Authors concluded that pathogenesis was evidently a combination of chronic absorption and the individual's hypersensitivity to inorganic mercury. Authors did also note that their patient did not display signs of acrodynia but did resemble a case of abortive acrodynia with mild polyneuritis, atypical extrapyramidal hyperkinesia, asynergia, eosinophilia, and albumin-cytologic dissociation in the CSF, after being treated with a mercury preparation rectally as an anthelmintic (Ross 1964).

In 2010, twin 13-year-old sisters were admitted for generalized body pain, especially in the extremities and back, and they complained of headache, chilling, and sweating (Khodashenas et al 2015). Noted was a 2 month history of pain in their legs, gradually causing them not to be able to walk to school. Anorexia, weakness, lethargy, excessive sweating, and salivation were also noted. Itchy rash on the body and extremities presented 2 weeks prior to hospital admission. On admission, the patients were irritable and depressed and had tachycardia without elevated blood pressure or body temperature. MRI of the brain and thighs and EMG/NCV testing were normal in both patients. Twenty-four-hour urine mercury concentration were measured and revealed toxic levels (50 and 70 ug/L). The mother later recalled using of a compound that contained mercury for the treatment of pediculosis 3 months prior to onset of symptoms. The compound was purchased from an herbal shop and was applied locally on the scalps for 2 days. The twins were treated with D-penicillamine (DPCN) 20 ug/kg/d orally in 4 divided doses. They were additionally treated with gabapentin (300 ug) orally in 3 divided doses for pain. After 2 weeks of therapy, 24-hour urine mercury concentrations had fallen to 9 to 15 ug/L, and the patients were discharged. Authors reported that the sisters' clinical presentation was compatible with acrodynia, characterized by dark pink discoloration and scaling of the hands and feet, weakness, pain, irritability, hypertension, tachycardia, peripheral neuropathy, recessive salivation, and sweating. That being said, authors concluded that when patients present with bone/joint pain, skin rash erythema, and peripheral neuropathy, mercury poisoning should always be included in the differential diagnosis.

A 54-year-old female with early onset dementia, epilepsy, and peripheral polyneuropathy was diagnosed with mercury intoxication in 2010, and she failed chelation therapy with 2,3-dimercaptopropane-1-sulfonate (DMPS) in 2013. EMG revealed chronic denervation in the tibialis anterior, but no follow up studies were performed. Following a detailed patient history, it was found that she had been using a mercury-containing skin lightening cream daily for 6 years. Treatment with 200 mg oral DMSA 3 times a day was initiated. Blood mercury levels fell from 13.3 to 5.2 ug/L. NSE levels fell from 31.4 to 20.5 ug/L, and urine mercury levels fell from 18.4 to 3.7 ug/L. Follow-up brain MRI showed unchanged brain lesions and 1 new lesion seen in the left temporo-occipital subcortical region. On discharge, however, memory function was improved qualitatively and quantitatively (Zellner et al 2016).

A diet heavy in shellfish, fish, and marine mammals from mercury contaminated waters may lead to high levels of blood mercury. The largest and oldest fish will have the highest levels of mercury. The U.S. Food and Drug Administration (FDA) has estimated the amount of mercury in a normal adult diet and found it not to be harmful. Literature has described that this risk is likely underestimated (Budtz-Jorgensen et al 2007). The 2014 Draft Advice by the U.S. Food and Drug Administration and Environmental Protection Agency has proposed updated cautions for women pregnant (or who might become pregnant) or breastfeeding, or those feeding young children on the consumption of fish associated with high mercury levels (U.S. Food and Drug Administration and U.S. Environmental Protection Agency 2016). Fish associated with high mercury levels are tilefish from the Gulf of Mexico, shark, swordfish, and king mackerel.

Other food sources of mercury exposure have also been identified. NHANES data combined with that from the U.S. Department of Agriculture’s Food Intakes Converted to Retail Commodities Database (FICRCD) examined 49 different food and environmental metal exposure. Using results from blood and urinary biomarkers, researchers estimated that 4.5% of the variation of mercury among children and 10.5% among adults is explained by diet. A previously unrecognized association between rice consumption and mercury exposure was found (Davis et al 2014). Latov and
colleagues identified that environmental sources may play a role in idiopathic axonal and small fiber neuropathy (see below) (Latov et al 2015).

**Various forms of mercury poisoning.** The various forms of mercury (organic mercury compounds, inorganic mercury salts, and elemental mercury) are all potentially neurotoxic and may produce different clinical pictures. They will be considered separately.

**Organic mercury poisoning and neuropathy.** Organic mercury is readily absorbed through the skin and gastrointestinal tract. Data concerning organic mercury (methylmercury) poisoning have come from accidental human exposures. Mercuric chloride is an inorganic compound used as an industrial catalyst. In the Japanese fishing village of Minamata, it was discharged into the sea for decades by an industrial plant and converted into methylmercury by microorganisms. It then entered the food chain and was concentrated in the bodies of fish and shellfish. These organisms served as staple items in the diet of the local population. It was observed that cats and seabirds, who also fed on the fish, were developing neurologic disease, leading to the identification of methylmercury as the toxin (Kurland et al 1960).

Paresthesias and sensory loss in stocking glove distributions were noted in the distal extremities of Minamata Bay inhabitants. Muscle atrophy was also reported and these symptoms appeared to have worsened over a 3 to 10 year period (Tamashiro et al 1985).

Another major outbreak arose in Iraq after grain treated with an ethyl mercury fungicide was used for baking bread (Kantarjian 1961; Bakir et al 1973). This grain had originally been intended for planting. In these cases, paresthesias were also observed (Evans et al 1977).

During chronic exposure to methylmercury, prominent central nervous system disease develops including visual fields constriction, ataxia, dysarthria, hearing loss, tremor, and cognitive impairment. One of the earliest complaints in many patients is distal paresthesia (Takeuchi 1977), which progresses proximally and may involve the tongue. This and ataxia are probably related to selective toxic effects on the neurons of the dorsal root and trigeminal sensory ganglia. Excretion of methylmercury is first-order in humans, and its half-life has been estimated to be roughly 70 days (Clarkson 2003). There may be a long latency period between time of exposure and the onset of neurologic symptoms; the reason for this latency is not clear (Nierenberg 1998).

**Dimethylmercury, a supertoxin, is lethal in doses of only a few drops, even if the exposure is brief. Exposure may occur via inhalation or transdermal absorption; typical disposable latex gloves do not provide protection against permeation. A tragic case of dimethylmercury poisoning occurred in 1996. A 48-year-old chemistry professor accidentally spilled drops of dimethyl mercury from her pipette onto the back of her latex glove. After a latent period of over 5 months, she developed a progressive cerebellar syndrome with gait ataxia, dysmetria, and scanning speech. Subsequently, she suffered progressive visual and hearing loss, paresthesias in the limbs, and encephalopathy. Despite 3 months of aggressive treatment, including chelation therapy with oral DMSA and exchange transfusion, she was left in a condition resembling a persistent vegetative state; life support was withdrawn in accordance with previous wishes (Nierenberg 1998).**

A link between thimerosal, an ethyl mercury-containing preservative used in vaccines, and autistic spectrum disorders has been suggested. There are no compelling studies to date, however, to substantiate these claims (Parker 2004). In 2002, the World Health Organization advisory committee deemed it safe to continue to use thimerosal in vaccines (Strategic Advisory Group of Experts 2002). Nevertheless, thimerosal-containing vaccines are no longer used in the United States, with the exception of influenza vaccines. Ingestion of a large dose of thimerosal in an adult led to multisystemic toxicities, including peripheral neuropathy, with subsequent recovery (Pfab 1996).

Le Quesne and associates evaluated 19 patients with organic mercury poisoning, 4 of whom were severe, and none demonstrated peripheral electrodiagnostic abnormalities, suggesting a CNS etiology for their complaints (Le Quesne et al 1974). Von Burg and Rustam evaluated Iraqis with poisonings and found no abnormalities. However, they did discover that patients responded better to neostigmine than placebo (Von Burg and Rustam 1974; Rustam et al 1975).

In 1981, a brief report described an increase in mercury vapor released into the breath by chewing (Svare et al 1981). Patients with silver mercury amalgam fillings were compared to patients without these fillings. The authors raised the question that biotransformation might occur, and low levels of ingested or inhaled mercury might be converted into
more toxic methylmercury. In spite of the lack of direct evidence for this biotransformation, the role of dental amalgam in the production of neurologic disease has repeatedly arisen. Cases have included peripheral neuropathy, dementing disorders, motor neuron diseases, and chronic fatigue syndrome. No published studies have ever been able to link amalgam fillings to neurologic disease, and no trial has ever demonstrated a benefit from removing fillings. After an intensive investigation and review of the evidence, the Public Health Service concluded in 1993 that dental amalgams did not pose a serious health risk (Kulig 1998). A study of 1663 middle-aged men found no detectable association between amalgam exposure and peripheral neuropathy (Kingman 2005). Shapiro, however, found 30% of dentists with raised tissue levels of mercury had electrodiagnostic evidence of reduced mean sural and median motor conduction velocities compared to dentists with normal tissue mercury levels, consistent with subclinical neuropathy (Shapiro et al 1982). For these reasons, it must be concluded that, at present, there is no evidence to link amalgam fillings to specific neurologic disease. Furthermore, the process of removal generates mercury vapor, raising mercury blood concentrations substantially before eventual decline (Clarkson 2003).

A paper by Latov and colleagues, evaluating blood levels of mercury by mass spectrophotometry in patients with idiopathic axonal and small fiber neuropathy, found increased incidence of elevated blood levels, which were suspected to be from ingestion of methylmercury in seafood (Latov et al 2015). Although cause or contribution to these neuropathies was not concluded, certainly more studies are warranted.

Inorganic mercury poisoning and neuropathy. It is difficult to separate the effects of elemental mercury from those of mercuric salts because most cases arise from occupational exposure to both forms (Berlin 1979). It is probable that inorganic mercury, because of its greater water solubility, is best absorbed through the gut; it produces prominent systemic as well as nervous system effects. Elemental mercury, with greater lipid solubility, may produce nervous system disease with almost no systemic disease.

Mercury salts are used in a number of industrial processes. The major route of absorption of these mercury salts is by way of the gastrointestinal tract. Mercuric sulfate has been found in traditional Chinese herbal medications, which have been implicated in cases of mercury neuropathy (Chu 1998). Gastrointestinal symptoms and a nephrotic syndrome may be prominent systemic features, especially in acute poisoning.

Inorganic mercury is used in the chloralkali industry. Peripheral nerve dysfunction, often motor more than sensory, was noted in the cases summarized. Albers and colleagues reported 138 chloralkali plant workers with long-term exposure to inorganic mercury vapor who were found to have elevated urine mercury levels, reduced sensation on quantitative testing, prolonged distal motor latencies, reduced sensory evoked response amplitudes, and increased likelihood of abnormal needle EMG findings. Subjects exposed to mercury for 20 to 35 years who had urine mercury levels greater than 0.6 mg/L demonstrated significantly less strength, poorer coordination, more severe tremor, more impaired sensation, and higher prevalence of Babinski and snout reflexes than controls. Subjects with polyneuropathy had higher peak levels of mercury than healthy subjects. Factory workers exposed to elemental mercury vapor with elevated urine mercury concentrations had prolonged motor and sensory ulnar distal latencies. Slowing of the median motor nerve conduction velocity was found to correlate with both increased levels of mercury in blood and urine and increased numbers of neurologic symptoms. Sensory deficits were found with short-term exposure to mercury vapor, whereas motor nerve impairment occurred with longer periods of exposure (Albers 1982; Albers and Bromberg 1995). Motor nerves appeared to be more affected than sensory nerves in a study by Singer in 1987 that assessed 16 workers with inorganic mercury exposure. Median motor NCV slowing correlated with mercury blood and urine as well as an increased prevalence of neurologic symptoms (Singer 1987).

In another study by Andersen and coworkers, chloralkali workers exposed to inorganic mercury vapor for an average of 12.3 years revealed a higher prevalence of reduced distal sensation, postural tremor, and impaired coordination than controls revealed (Andersen et al 1993).

Barber reported 2 employees of a chloralkali plant who had findings suggestive of amyotrophic lateral sclerosis (Barber 1978). Signs, symptoms, and laboratory findings returned to normal 3 months after withdrawal from exposure.

Adams and associates reported a 54-year-old man with a brief but intense exposure to mercury vapor, which led to a syndrome resembling amyotrophic lateral sclerosis that resolved as urinary mercury levels fell (Adams et al 1983). Ross reported that prolonged application of an ammoniated ointment to the skin was a cause of motor polyneuropathy with cerebrospinal fluid findings suggestive of Guillain-Barré syndrome.
Warkany and Hubbard reported the association of acrodynia and symmetrical flaccid paralysis with mercury toxicity (Warkany and Hubbard 1953).

Chloralkali workers who were exposed to inorganic mercury for an average of 7.9 years and had ceased working in that environment an average of 12.3 years prior to the study were found to have both median sensory nerve conduction velocities and amplitude of the sural nerve associated with measures of cumulative exposure to mercury (Andersen et al 1993; Ellingsen 1993). A study reviewing the relationship between exposure-related indices and neurologic and neurophysiologic effects in workers previously exposed to mercury vapor revealed that, of 298 dentists with long-term exposure to mercury amalgam vapor evaluated for peripheral neuropathy, 30% had polyneuropathies (Shapiro 1982). Another paper reported that a dentist apparently had an unelicitable sensory superficial peroneal nerve action potential that returned to normal following penicillamine treatment (Iyer et al 1976).

Industrial workers with long-term exposure to mercury were found to have performance decrements in neuromuscular functions that were reversible and correlated with blood and urine mercury levels (Berlin 1979).

Dentists were assessed during continuing medical conferences and tested for urine mercury and median and ulnar sensory nerve distal latencies (Franzblau 2012). No associations were found.

**Elemental mercury poisoning.** Acute inhalation of elemental mercury vapor can cause irritation to the upper respiratory tract causing acute pneumonitis, bronchitis, and bronchiolitis and is commonly mistaken for viral infection if not properly diagnosed (Bluhm et al 1992).

Chronic inhalation of elemental mercury may cause adverse health effects if exposure is above the minimal risk level of 0.3 μg/m³ (Agency for Toxic Substances and Disease Registry 1999). Clinical presentations are subtle and typically considered insignificant. Complaints include fatigue, general weakness, lack of appetite, diarrhea, lack of sleep, change in mood, and tremor, which has been called “micromercurialism” (Friberg and Nordberg 1972). The tremor is described as being fine and rapid, worsens with activity and emotional excitement, and resembles the tremor seen in patients with hyperthyroidism. The tremor frequency, however, is faster and differs from the characteristic resting pill-rolling seen in Parkinson patients (Feldman 1998).

Elemental mercury is absorbed poorly from the gastrointestinal tract; swallowing mercury is not known to be harmful. Metallic mercury is volatile at room temperature. A saturated atmosphere of mercury vapor contains 18 mg of Hg per cubic meter at 24 degrees Celsius. Friberg and Nordberg have demonstrated that chronic Hg exposure to levels above 0.1 mg/m³ in air is associated with the development of toxicity (Friberg and Nordberg 1972). This level is of particular significance because small quantities of metallic mercury may remain hidden for long periods of time in poorly ventilated areas. Because of its greater lipid solubility, toxicity often manifests first by central nervous system symptoms of fatigue associated with weight loss, anorexia, and gastrointestinal dysfunction. With higher exposure, personality and behavioral changes, insomnia, and hyperexcitability develop, often associated with a coarse facial, head, and limb tremor. A few cases of predominantly peripheral nervous system involvement associated with exposure to organic and elemental mercury have been recorded (Ross 1964; Swaiman and Flagler 1971; Windebank and Dyck 1986). Elemental mercury exposure from broken school barometers led to symptoms and signs of mercury toxicity in 3 teenagers; all 3 had secondary hypertension, and 2 of the 3 developed peripheral neuropathy and CNS involvement (Koyun 2004).

Seventeen thermometer factory workers with no neurologic complaints had high urine and blood mercury levels but no symptoms; 14 had subclinical neuropathy, mainly distal and axonal neuropathy (Zampollo et al 1987).

Levine and associates, in 1982, studied right ulnar nerve NCVs in factory workers with elemental mercury exposure (Levine et al 1982). Prolonged motor and sensory distal latencies were correlative with increasing urine mercury levels.

Albers and colleagues evaluated 386 chloralkali workers with 20 to 35 years of elemental mercury exposure and uncovered prolonged sensory and motor distal latencies in those workers whose biological monitoring revealed urine mercury concentrations above 600 ug/L (Albers et al 1988). EMG was also performed and was noted to show an increased prevalence of abnormal electrical activity.

Authors in the United States reported that a patient developed gait ataxia, diplopia, and vomiting 1 year after self-injection of elemental mercury during a cultural practice (Malkani et al 2011). He was found to have an indurated plaque on his right shoulder along with cranial neuropathies. Urine mercury was elevated. CSF revealed pleocytosis.
After excision of the skin lesion, a reservoir of mercury, and chelation, he experienced mild improvement. 

In 2013, Turkish authors reported 179 children were exposed to elemental mercury in schools in 2 different provinces of Turkey (Carman et al 2013). Children took the mercury home and invited others play with it. Some boiled the material, heated it, and even tasted it. Median exposure duration was 5 minutes, but some played for 24 hours. Fifty-one percent were asymptomatic, and 44% had a normal neurologic examination. Thirty percent had headache, and 5.5% had symptoms of peripheral neuropathy with normal NCV and EMG. MRIs of the brains were normal. Duration of exposure was correlated with elevated urine mercury. Pupillary dilatation was noted as the most common exam finding. After 6 months, peripheral neuropathy symptoms resolved.

A paper from the Netherlands reported that a family was exposed to 3 ml of mercury from a broken barometer in a home. Blood mercury was 32 ug/L in a 9-month old infant and 26 ug/L in a 2-year old child at 6 hours post incident. A babysitter was found to have a blood mercury of 20 ug/L. Indoor air over the next 3 months was monitored. No health complaints were observed in any of the individuals.

Prognosis and complications

The prognosis for recovery from peripheral nervous system involvement is good, although deficits may persist in severe cases (Chu 1998). CNS injury is usually permanent.

Biological basis

Etiology and pathogenesis

The cause of disease may be an occupational, accidental, or suicidal exposure to mercury compounds. Industrial uses of mercury, including the manufacture of batteries, latex paint, urethane, and polyvinyl chloride; fossil-fuel plants, incinerators, and municipal sewage systems as well as industrial discharge into rivers and streams may all lead to environmental pollution with mercury. Indeed, everyone is exposed to mercury in some form, whether from a source listed above or from thimerosal- or phenylmercuric nitrate-containing pharmaceuticals, fish consumption, or dental amalgams. Due to its accumulation in the food chain, chronic exposure to methylmercury via consumption of fish and sea mammals is still a major concern for human health, especially developmental exposure that may lead to neurologic alterations, including cognitive and motor dysfunctions (Ceccatelli et al 2010). Thus, it is common to be able to detect mercury in blood, hair, and nails of normal people (Kulig 1998). Specific sources of accidental mercury exposure are quicksilver used in ethno-religious ceremonies common in some Hispanic and Caribbean communities, paint fumes from phenylmercuric acetate-containing interior latex paint, broken mercury-containing barometers or thermometers, Chinese herbal-ball preparations (Espinoza 1995; Chu 1998), mercurial skin-lightening soaps and creams, spilled elemental mercury from pressure gauges, mercury inhalants used in gold recovery methods, ammoniated mercury ointments for the treatment of eczema or psoriasis (Kern 1991; Pelclova 2002), teething compounds (Weinstein 2003), diaper powders, and broken fluorescent light bulbs.

Following the outbreak of methylmercury intoxication in Minamata, extensive pathologic reports were published. These primarily involved the central nervous system, where prominent atrophy and degeneration of the cerebellar and calcarine cortex are seen (Takeuchi 1977). In the peripheral nerves of humans, axonal degeneration in the sural nerve and lumbar dorsal roots has been demonstrated (Takeuchi and Eto 1977). In experimental animal studies, the major pathologic change appears to be axonal degeneration without segmental demyelination. This has been shown in the L6 dorsal roots of rats but not in the ventral roots. The rate of axonal degeneration in the sural nerve is the same at mid-thigh and ankle level; therefore, the dorsal root ganglion cell is thought to be the primary site of action in the peripheral nervous system (Miyakawa et al 1970). Somjen and colleagues have demonstrated in rats that methylmercury administration resulted in a reduction of the compound action potential evoked in dorsal roots, whereas the ventral root action potential was virtually normal (Somjen et al 1973a; Somjen et al 1973b). This physiologic action was correlated with the finding that the major site of uptake of radioactive 203 Hg methylmercury in the peripheral nervous system was the spinal dorsal root ganglia. In a rat model study, both methylmercury and mercury vapor produced selective degeneration of dorsal root ganglia and dorsal nerve roots (Schionning et al 1997; Schionning et al 1998). The number of autopsy cases for Minamata disease has risen (Eto et al 2002). In one case autopsy, the dorsal roots and sural nerve showed endoneurial loss of nerve fibers, and presence of Büngner bands. The spinal cord showed Wallerian degeneration of the fasciculus gracilis (Goll tract) with relative preservation of neurons in sensory ganglia. These findings support the contention that there is peripheral nerve degeneration in
Minamata patients due to toxic injury from methylmercury.

Thus, in both humans and animals, it appears that the major pathologic effect of methylmercury is on the dorsal root ganglion cells. In experimental models, it was found that the sensory neurons in the spinal ganglia and granule cells in the cerebellum were most vulnerable to mercury poisoning. Ultrastructural studies indicated that vacuolar degeneration of the neurons was mainly associated with inorganic mercury intoxication, whereas the coagulative type of degeneration was found mostly in organic mercury poisoning. Degenerative changes in the nerve fibers were also observed. Based on the biochemical, physiological, and pathological findings on mercury intoxication, a working hypothesis on the pathogenetic mechanism of mercury on the nervous system is proposed (Chang 1990). No similar data are available for inorganic or metallic mercury poisoning. Because of the different chemical properties and clinical manifestations, it is likely that these latter compounds exert their action at a different site. Three major mechanisms have been identified as critical in methylmercury-induced cell damage, including (i) disruption of calcium homeostasis, (ii) induction of oxidative stress via overproduction of reactive oxygen species or reduction of antioxidative defenses, and (iii) interactions with sulfhydryl groups (Ceccatelli et al 2010).

Epidemiology"

Epidemiological investigation was important in identifying environmental contamination with organic mercury compounds, like the Minamata Bay outbreak (Kurland et al 1960; Yoshida et al 1992). Mercury compounds should be considered as possible causative agents in any outbreak of unknown neurologic disease if it involves prominent cerebellar findings.

Prevention

Effective treatment involves removing the source of exposure. Exposure to mercury vapor may occur accidentally in the home. This has occurred when liquid mercury is spilled, either by accident or in situations such as ethno-religious ceremonies. Danger is greatest when exposure occurs in poorly ventilated areas. The vapor is heavy, layering close to the floor. Infants and children, who breathe closest to the floor and often play on the ground, are at greatest risk (Clarkson 2003). If there is any suspicion that mercury vapor exposure may be occurring, air levels should be monitored. Disposable monitors are available through public health departments. If toxic levels (greater than 0.1 mg/m³) are present, subjects should be removed to well-ventilated areas and the source of mercury vapor identified and removed.

Differential diagnosis

Mercury intoxication usually involves the subacute onset of mood and intellectual changes, followed by tremor and other signs suggestive of spino-cerebellar involvement. There may also be significant constriction of visual fields. Differential diagnosis would include subacute cerebellar degeneration as a paraneoplastic syndrome, multiple sclerosis, and the cerebellar form of Creutzfeldt-Jakob disease. In long-term or chronic exposure with a slowly progressive course, mercury intoxication might resemble spino-cerebellar degeneration. There is 1 case report of mercury intoxication initially mimicking amyotrophic lateral sclerosis (but with subsequent recovery) after a brief, intense exposure to elemental mercury (Adams 1983). Mercury toxicity may resemble renal artery stenosis or rarer causes of secondary hypertension, such as pheochromocytoma or neurofibroma, because mercury binds and inactivates S-adenosylmethionine, an enzyme involved in catecholamine catabolism (Beck 2004).

When considering whether a patient's neuropathy arises from occupational or environmental toxicity, one should consider the following algorithm.

Table 1. Algorithm for Clinical Assessment of Neurotoxic Disease

- Begin the evaluation by noting the chief complaint or complaints. Consider when they began and how they relate to an exposure.
- Take a thorough medical history that includes an occupational and environmental history to consider all sources of exposure to all possible agents. List details of all jobs and job tasks within the jobs and what symptoms and medical problems began when.
- Consider review of systems and how eating, bowel movements, sexual activity, sleep, and emotional status varied during exposure incidents.
• List medical complaints on a timeline and relate each to known exposure dates, duration, and intensity. Consider other occupational, environmental, and drug exposures. Include vitamin supplements, hobbies, and traditional practices.
• Include birth history, pregnancy, and extensive family history to uncover any genetic or congenital diseases.
• Consider how symptoms change as they relate to exposures. How often do flare-ups occur? Are the symptoms persistent or do they improve?
• Do colleagues or coworkers have similar complaints?
• List all potential sources of exposure: from where, what form, and how they are used.
• Obtain Material Safety Data Sheets and scientific data on each unfamiliar chemical agent.
• Perform neurologic examination. A general medical examination including an assessment of the autonomic system, hair, teeth, nails, skin color, and lymph system is important. Are any objective neurologic signs or other systemic findings noted?
• Arrange for appropriate confirmatory neurophysiological, neuropsychological, and imaging tests.
• Arrange for serum and biological monitoring when appropriate.
• Review regulatory information for mercury. What have OSHA, EPA, NIOSH, American Conference of Governmental Industrial Hygienists (ACGIH), and other international organizations published as a safe level?
• Consider contacting an industrial hygienist for air and water sampling, if relevant.
• Consider removal from exposure.
• Consider whether exposure and medical problem may be consistent chronologically. First, did the exposure precede the complaint or dysfunction?
• Exclude all other common causes of the diagnosis. Are the findings consistent with a primary neurologic or other medical condition? Are the findings explained by other historical or familial factors? Other exposures, illnesses, or stressors?
• Search literature for epidemiologic and case studies and series that describe an association between exposure and dysfunction.
• Is dose and duration of exposure consistent with the described dysfunction? Focus on details of the literature.
• What is the proposed mechanism for this exposure-induced dysfunction?
• Estimate functional status and medical treatment options and consultation necessary for support.
• Reevaluate by examination and neurologic and neuropsychological tests. Do the results remain consistent?

(Feldman and White 1996; Rutchik 2007)

**Diagnostic workup**

The diagnosis of mercury intoxication depends on the demonstration of an appropriate neurologic syndrome in the context of exposure of mercury or mercury compounds. If there are symptoms or signs of neuropathy, nerve conduction studies and needle electromyography should be performed. Typical findings are that of a sensorimotor axonal neuropathy; myokymia may sometimes be encountered. EMG needle examination may show chronic neurogenic changes, which are most notable in the intrinsic foot muscles (Little and Albers 2015). In the case of methylmercury intoxication, circumstantial evidence may be the only form available because the compound has such a high affinity for the nervous system that neurologic disease may be present in the absence of elevated urine mercury levels.

In the case of inorganic or metallic mercury intoxication, this can usually be confirmed by measurement of 24-hour urinary mercury excretion using flameless atomic absorption spectrophotometry or mass spectroscopy. Mercury is excreted slowly from the body. The biological half-life for mercury excretion differs depending on its form; ethyl
mercury is estimated to have a half-life of 20 days, whereas inorganic divalent mercury, mercury vapor, and methylmercury are estimated to have a half-lives of 40, 60, and 70 days, respectively (Clarkson 2003). At the Mayo Clinic trace metal laboratory, the mean level for nonexposed individuals is 5 mcg per 24-hour period. Occupationally exposed individuals may excrete 25 to 30 mcg per 24-hour period; levels above 50 per 24 hours raise the question of toxicity related to mercury exposure. It is important to note that blood mercury may be best to assess organic mercury, whereas urine mercury best assesses inorganic or elemental mercury exposures.

Biological testing of serum and urine to assess absorbed dose may be compared to values published for these data. These data suggest that urine or blood levels are associated with health effects for mercury exposure.

Table 2. ATSDR Biological Exposure Indices (BEIs)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Urine: start of shift</th>
<th>Blood: end of shift at end of work week</th>
<th>Expired Air</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury, inorganic</td>
<td>35 µg/g</td>
<td>15 µg/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When occupational exposure occurs, industrial hygiene data may be helpful. The Occupational Safety and Health Administration (OSHA), the National Institute of Safety and Health (NIOSH), and the American Congress of Governmental Industrial Hygienists (ACGIH) are useful resources from which to compare the workers inhalation exposure. Estimating dose and duration of exposure and level of protection afforded by personal protective equipment is emphasized. Government and professional organizations publish exposure limits for workers using various chemicals. Physicians may use this information to compare with industrial hygiene data (Feldman 1991; LaDou 1997; Feldman 1998; Rutchik 2007; Rutchik 2009a; Rutchik 2009b; Rutchik 2009c).

Table 3. Published Limits for Mercury Exposure

<table>
<thead>
<tr>
<th>Compound</th>
<th>OSHA PEL TWA: ppm (mg/m3)</th>
<th>NIOSH REL TWA: ppm (mg/m3), IDLH</th>
<th>ACGIH ppm (mg/m3) TLV, STEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury, inorganic</td>
<td>C 0.1 mg/m3 (construction)</td>
<td>0.05 mg/m3, C 0.01 mg/m3, 10 mg/m3</td>
<td>0.025 mg/m3</td>
</tr>
<tr>
<td>Mercury, organic</td>
<td>0.01 mg/m3, C 0.04 mg/m3</td>
<td>ST 0.03 mg/m3, 2 mg/m3</td>
<td>0.01 mg/m3, 0.03 mg/m3</td>
</tr>
</tbody>
</table>

Abbreviations: OSHA - Occupational Safety and Health Association; NIOSH - National Institute of Occupational Safety and Health; ACGIH - American Congress of Governmental Industrial Hygienists; TWA - time-weighted average; TLV - threshold limit value; PEL - permissible exposure limit; REL - recommended exposure limit; ppm - parts per million; STEL - short-term exposure limit; C - ceiling, should never be exceeded

(Feldman 1991; Feldman 1995; Feldman 1998; Bleeker 1994; LaDou 1997; Rutchik 2007; Rutchik 2009a; Rutchik 2009b; Rutchik 2009c).

Management

Treatment for mercury neurotoxicity includes chelating agents British anti-Lewisite (BAL), meso-2,3-dimercaptosuccinic acid (DMSA), D-penicillamine (DPCN), and oral 2,3 dimercapto 1 propanesulfonate (DMPS). These have been used in cases where dramatic neurotoxicity is confirmed from mercury exposure.

Animal experiments support a role for chelation in acute exposure cases and should be instigated promptly in such cases. Efficacy declines or disappears as the time interval between metal exposure and onset of chelation increases (Kosnett 2013). Side effects include hypersensitivity, renal effects, and aplastic anemia. Hemodialysis may also be used in cases where renal function is compromised. L-cysteine may significantly improve the ability of hemodialysis to remove circulating mercury. DMSA taken orally has been approved by the U.S. Federal Drug Administration (FDA) for the treatment of mercury poisoning (Mutter and Yeter 2008), and it is the only chelator that has been approved by the FDA for treating mercury poisoning in children (Khodashenas et al 2015).

DMSA and DMPS are found to be less toxic and more efficient than BAL in the treatment of heavy metal poisoning and are available in capsules for oral use (Aaseth et al 2015). These agents also do not redistribute mercury to the brain or accelerate excretion, but a decrease in morbidity and mortality is not clearly established for cases of chronic intoxication (Kosnett 2013).
With inorganic mercury intoxication, for those who do not respond quickly to removal from the source of the exposure (Feldman 1995), chelation with oral DMPS has been dramatically helpful in individual and case series. Bradberry and colleagues reported reversal of neurologic damage with a 5-day course of DMPS chelation in a jeweler who presented with a 1-year progressive neurologic syndrome after 5 years of exposure to mercury vapor (Bradberry et al 2009).

Chelation may be appropriate for patients with inorganic mercury intoxication who do not respond quickly to removal from the source of the exposure (Feldman 1995). Chelation is rarely accomplished unless toxicity is present from acute occupational exposure that is confirmed by an occupational and environmental medicine physician or toxicologist.

There are practitioners in many communities who perform chelation routinely on patients with vague symptoms, but the literature has not supported this treatment. Chelation was successful in treating 1 patient who attempted suicide with mercuric chloride (Brodkin et al 2007; Wang et al 2007).

**Special considerations**

**Pregnancy**

Methylmercury inhibits migration and division of neurons and disrupts the cytoarchitecture of the developing brain, placing the fetal brain at greater risk of suffering from mercury toxicity (Clarkson 2003). Prenatal methylmercury exposure, however, has not been linked to subsequent neuropathy. A developmental study of children in the Seychelles Islands, whose mothers had methylmercury ingestion via fish consumption, found no evidence of neurotoxicity related to this exposure (Lapham 1995). A pregnant woman who consumed pork from a pig fed methylmercury-treated seed grain gave birth to a child with signs of CNS mercury toxicity; peripheral neuropathy was not clearly described (Davis 1994). Furthermore, elemental, inorganic, and organic mercury are excreted in breast milk, and therefore, children who are breastfed by women exposed to mercury may also be exposed to potentially toxic amounts of mercury (Feldman 1998).

**References cited**


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**References especially recommended by the author or editor for general reading.

Former authors

Tony J Windebank MD (original author) and Robert W Pratt MD

ICD and OMIM codes

ICD codes

ICD-9:
Toxic effect of mercury and its compounds: 985.0
Poisoning by heavy metal anti-infectives: 961.2
Polyneuropathy due to other toxic agents: 357.7
Accidental poisoning by mercury and its compounds and fumes: E866.1
Heavy metal anti-infectives causing adverse effects in therapeutic use: E931.2

ICD-10:
Toxic effects of mercury and its compounds: T56.1
Assault by other specified chemicals and noxious substances: X89.09
Polyneuropathy due to other toxic agents: G62.2
Accidental poisoning by mercury and its compounds and fumes: X49.09
Other specified systemic anti-infectives and antiparasitics: Y41.8

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

none

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

subacute cerebellar degeneration as a paraneoplastic syndrome
multiple sclerosis
cerebellar form of Creutzfeldt-Jakob disease
spinocerebellar degeneration
amyotrophic lateral sclerosis
renal artery stenosis
secondary hypertension
pheochromocytoma
neurofibroma
glucose dysmetabolism

Associated disorders

Minamata disease
Myokymia

Other topics to consider

Chelation therapy
Heavy metal exposure
Introduction to toxic peripheral neuropathies
Occupational and environmental encephalopathies: heavy metals