

# Mercury and Movement Disorders: The Toxic Legacy Continues

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**ABSTRACT:** Mercury (Hg) exists in the environment as inorganic (metallic Hg vapor, mercurous and mercuric salts) or organic (bonded to a structure containing carbon atoms) forms. Neurotoxic effect of Hg is known for years. While the organic form (methylmercury (meHg)) led to the Minamata incidence in Japan and “wonder-wheat” disaster in Iraq, the “mad hatters” and “Danbury shakes” were related to the inorganic elemental form (Hg vapor). Human exposure to toxic Hg continues in the modern world to a large extent by artisanal gold mining, biomass combustion, chloralkali production, and indigenous medicine use to name a few. Heavy industrial use of Hg contaminates air and landfills, affecting the aquatic ecosystem and marine food chain. A detailed social and occupational history with a high index of clinical suspicion is required to not miss this toxic etiology for movement disorders like ataxia, tremor, or myoclonus. In this review, we have discussed the past and present global health impact of Hg from a movement disorder perspective. The connection of Hg with neurodegeneration and autoimmunity has been highlighted. We have also discussed the role of chelating agents and the preventive strategies to combat the neurotoxic effects of Hg in the modern world.

**RÉSUMÉ :** **Mercurie et troubles du mouvement : un héritage toxique toujours présent.** Le mercure existe dans la nature sous forme inorganique (par exemple des vapeurs de mercure métallique, des sels mercuriques ou des sels mercurieux) ou organique quand il est lié à une structure contenant des atomes de carbone. L'effet neurotoxique du mercure est connu depuis de nombreuses années. Alors qu'une forme organique (le méthyl-mercure) a conduit à une vaste contamination dans la ville japonaise de Minamata et est responsable de la contamination de semences de blé distribuées en Iraq, les syndromes des « chapeliers fous » et de Danbury étaient liés à une forme élémentaire inorganique (des vapeurs de mercure). Dans le monde moderne, l'exposition humaine au mercure se poursuit dans une large mesure, pour ne citer que quelques exemples, par l'extraction artisanale de l'or, la combustion de la biomasse, la production de chlore et de soude et le recours à des médecines indigènes. On le sait, l'utilisation industrielle lourde du mercure contamine l'air et les décharges, ce qui affecte en retour l'écosystème aquatique et la chaîne alimentaire marine. Chose certaine, une histoire détaillée des sociétés et des professions, de même qu'une excellente capacité de discernement clinique, sont nécessaires pour ne pas négliger l'étiologie toxique de troubles du mouvement tels que l'ataxie, les tremblements ou les myoclonies. Dans cet article, nous avons voulu discuter de l'impact passé et actuel du mercure sur la santé mondiale du point de vue des troubles du mouvement. Nous avons ainsi mis en évidence le lien existant entre le mercure et la neuro-dégénérescence et l'auto-immunité. Nous avons également discuté du rôle des agents chélateurs et des stratégies préventives pour combattre les effets neurotoxiques du mercure dans le monde moderne.

**Keywords:** Mercury, Cerebellar ataxia, Tremor, Myoclonus, Parkinsonism, Autoimmune movement disorder

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## INTRODUCTION

Mercury (Hg) is a nonessential element for the human body. Hg is emitted into the environment and released into landfill and water systems from anthropogenic activities or natural sources. Expanded industrial use of Hg has exposed a large population to its neurotoxic effects. Hg exists as elemental (vapor), inorganic (mercuric salts, when elemental mercury combines with sulfur, chlorine), and organic salts (when elemental mercury combines with carbon, e.g. methylmercury (meHg)).<sup>1</sup> Elemental mercury affects humans via occupational (Hg vapor) or environmental exposure (air pollution), whereas MeHg comes mainly from the aquatic marine food chain. As our society has advanced, modes

of human exposure to Hg have changed, but it is still very much relevant and necessary not to forget this as a risk factor for movement disorders like cerebellar ataxia, tremor, and myoclonus. Failure to recognize this toxic etiology often leads to unnecessary investigations and misdiagnosis. There is also evidence suggestive of the possible link of Hg with parkinsonism and autoimmune movement disorders. The studies on Hg and movement disorders have investigated heterogeneous patient populations with a diverse source of exposure. In this review, we have consolidated the literature on human exposure to Hg and movement disorders, along with their pathophysiological basis and the preventive strategies.

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## LITERATURE SEARCH

The literature search was conducted using four databases: PubMed, ScienceDirect, Cochrane Library, and BioMed Central (January 1930 to December 2020) using keywords “mercury and neurology”, “mercury and movement disorders”, “mercury and tremor”, “mercury and ataxia”, and “mercury and parkinsonism”. Duplicates were removed. Articles highlighting mainly the movement disorder perspective from human exposure to Hg were included. A consolidated overview has been extracted from them and presented in this review.

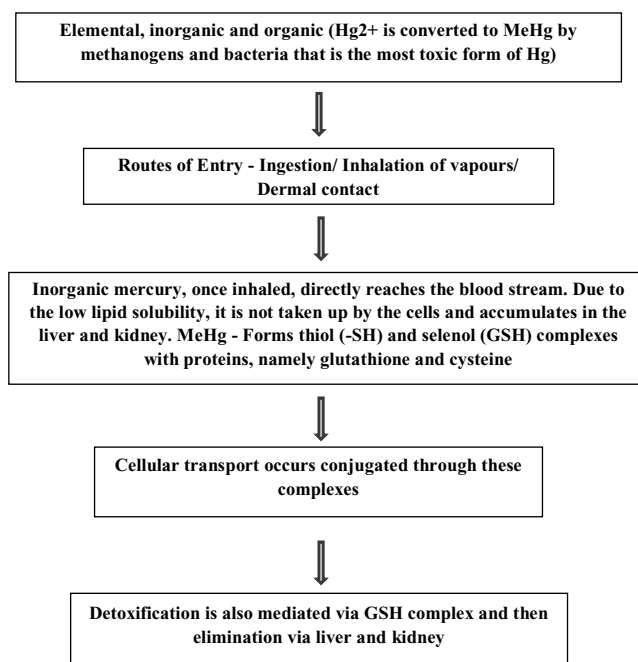
In the following sections, we have first discussed biochemical properties of Hg and pathophysiology of neurotoxicity, followed by major sources of human exposure and movement disorders related to Hg exposure.

## Biochemistry and Pathophysiology

Elemental mercury ( $\text{Hg}^0$ ) vaporizes at room temperature and enters into the body via an inhalational route. It can cross the blood–brain barrier (BBB) to cause neurotoxicity. In the blood-stream,  $\text{Hg}^0$  is oxidized to mercuric ion ( $\text{Hg}^{2+}$ ) by the catalase enzyme.  $\text{Hg}^{2+}$  by itself cannot cross the BBB, though it can interact with intracellular enzymes, transporters, ion channels, and glutathione and paralyze the detoxification machinery. Urine and feces are the main excretory routes for elemental mercury.<sup>2,3</sup> Organic MeHg, on the other hand, intoxicates the marine ecosystem and affects humans mainly via the aquatic food chain. MeHg is almost 95% absorbed from the intestine. Subsequently, it forms complexes with thiol (-SH) and selenol (-SeH) groups and circulates to various organs including the central nervous system. MeHg-L-cysteine complex is transported across the BBB by the L-type amino acid transporters and is the main culprit for neurotoxic effects.<sup>3</sup> In the brain, glutathione complexes with MeHg for detoxification. MeHg complex gets excreted through the bile, kidney, and finally as mercuric Hg via feces [Figure 1]. Human exposure to elemental and organic mercury is highlighted in Figure 2.

MeHg-induced neurotoxicity is mainly related to four interrelated cellular events: (i) affection of GSH antioxidant system; (ii) glutamate dyshomeostasis; (iii)  $\text{Ca}^{2+}$  dyshomeostasis; and (iv) increased reactive oxygen species (ROS) generation and oxidative stress.<sup>4</sup> MeHg is highly toxic to the granule cells in the cerebellum while the Purkinje cells are relatively refractory. Though this specificity for granule cell pathology is unclear, differential expression of  $\text{GABA}_A$  receptor subunits ( $\alpha 6$   $\text{GABA}_A$  receptor subunits on granule cells and  $\alpha 1$  on the Purkinje cells) and NMDA subunits have been postulated (higher NMDAR2 expression in granule cells and NMDAR1 in Purkinje cells) as the likely causes.<sup>5,6</sup>

Hg-induced oxidative stress, disruption of neurotransmitter metabolism, excitotoxicity, neuroinflammation, selenium depletion, interaction with microtubules, altered membrane transport, and genetic susceptibility are hypothesized as possible etiological factors for neurodegeneration due to Hg exposure.<sup>7–10</sup> In mouse models, MeHg has been shown to decrease the number of neurites and alter the cytoskeletal structure in dopaminergic neurons.<sup>11</sup> Using a dopaminergic cell line, Shao et al. have demonstrated that MeHg can affect dopaminergic signaling in a way similar to 1-methyl-4-phenylpyridinium ( $\text{MPP}^+$ ).<sup>12</sup>  $\text{MPP}^+$  and MeHg both can alter the expression of genes involved in



**Figure 1:** Uptake and transport of mercury in the body.

dopaminergic signal transduction pathway like dopa decarboxylase (DDC), PARK2, PARK7, SLC6A3, synuclein alpha (SNCA), and tyrosine hydroxylase (TH).

Hg can also trigger the production of proinflammatory factors like interferon-gamma ( $\text{IFN-}\gamma$ ), tumor necrosis factor ( $\text{TNF-}\alpha$ ), interleukin 1  $\beta$  ( $\text{IL-1}\beta$ ), and autoantibodies.<sup>13</sup> Loss of tolerance to self-antigens, change in autoantigen fibrillar, activation of type 2 T helper cell (Th2) response, production of proinflammatory cytokines, stimulation of Cathepsin B activity, and induction of VEGF and IL-6 have all been attributed to the possible link between Hg and autoimmunity.<sup>14</sup> Genetic polymorphisms in Glutathione S-transferase family (GSTs), metallothioneins (MTs), selenoproteins, ATP-binding cassette transporter superfamily (ABCs), organic anion transporters (OATs), L-amino acid transporters (LATs), and APOE  $\epsilon 4$  allele are likely responsible for differential body handling of Hg in susceptible individuals after environmental exposure.<sup>15</sup> Pathophysiology of Hg-induced movement disorders has been summarized in Table 1.

## Human Exposure to Mercury

The use of Hg can be found in the history of medicine and alchemy of the ancient Egyptian, Greek, Roman, Chinese, and Hindu civilizations.<sup>16</sup> Hg was used by the ancient Egyptians and archeologists have found Hg in an Egyptian tomb dating to 1500 BC. The alchemists wondered about the mystical properties of Hg and used it to transmute base metals into gold. For alchemy, the Hindus used the word “Rasasiddhi” that means “knowledge of mercury”, with a belief that Hg was at the core of all metals and correct combination of Hg and other ingredients can yield gold. Gradually, the distinction between alchemy and medicine became blurred and cinnabar (mercuric sulfide) started being misused as an elixir of life to confer longevity or immortality. Reports of the therapeutic use of Hg and its compounds in syphilis are available from the 15th

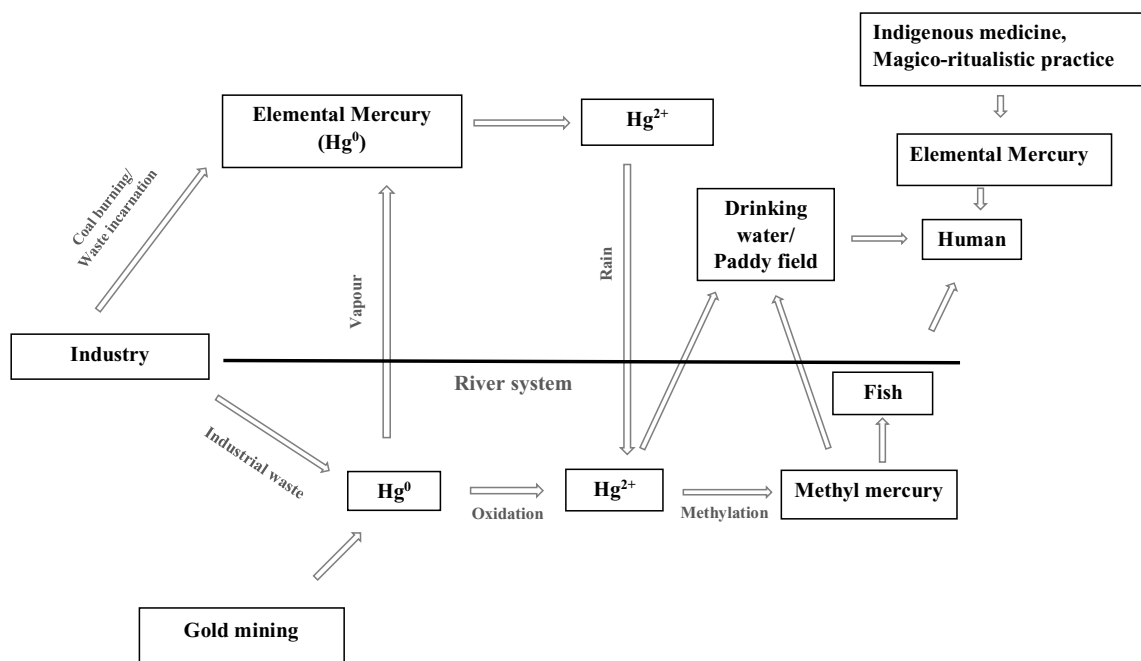


Figure 2: Human exposure to elemental and organic mercury.

Table 1: Pathophysiology of mercury-induced movement disorders

Mercury-induced movement disorders	Pathophysiology
Cerebellar ataxia and tremor	Toxic effect on granular cell layer of cerebellum due to – <ul style="list-style-type: none"> <li>Affection of GSH antioxidant system</li> <li>Glutamate dyshomeostasis</li> <li>Ca2+ dyshomeostasis</li> <li>Oxidative stress</li> </ul>
Myoclonus	<ul style="list-style-type: none"> <li>Loss of cerebellar motor cortex inhibition (CBI)</li> </ul>
Parkinsonism	<ul style="list-style-type: none"> <li>Toxic effect on dopaminergic neurons due to oxidative stress and excitotoxicity, mitochondrial dysfunction</li> <li>Altered expression of genes involved in dopaminergic signal transduction pathway</li> </ul>
Autoimmune movement disorders like Morvan syndrome	<ul style="list-style-type: none"> <li>Triggering production of proinflammatory cytokines</li> <li>Activation of type 2 helper T cell response</li> </ul>

century till as late as the mid 20th century.<sup>17</sup> With the advent of industrialization in 19th century, the toxic effects of Hg started affecting humanity in different parts of the world [Table 2]. An age-old source of Hg intoxication is the amalgamation technique, mainly used for gold extraction and the tradition is still being followed in many countries. The ore on being mixed with water, salt, and liquid Hg bind to the metal as an Hg–gold amalgam complex that releases Hg vapors if heated, leaving behind the gold particles. These vapors are an important source of inhalational Hg toxicity from ancient times and the metallic

form is released into the rivers and carried downstream, becoming another major source of toxicity.<sup>18,19</sup> Aquatic ecosystem and marine food chain are getting affected by the toxic waste of Hg even today. The Global Mercury Assessment 2018 (GMA 2018) conducted by the United Nations has shown that artisanal and small-scale gold mining (ASGM) (37.7%), stationary combustion of fossil fuel and biomass, especially coal (21%), nonferrous metals production (15%), and cement production (11%) are currently the four main sources of Hg emission. Major sources of Hg exposure in the modern world are shown in Table 3.

Human exposure to Hg can have toxic effects on cardiovascular (cardiomyopathy), hematological (hemolytic and aplastic anemia), renal (acute tubular necrosis, nephrotic syndrome, glomerulonephritis, chronic kidney disease), pulmonary (bronchitis, pulmonary fibrosis), immunological (affecting polymorphonuclear leukocytes, flaring up autoimmunity), endocrinal (hypoadrenalism, hypopituitarism, diabetes mellitus, hypothyroidism), reproductive (reduced fertility, menstrual disorders), embryonic (neural tube defects, craniofacial malformations, growth retardation), and neurological (movement disorders, psychiatric issues, autism, peripheral sensory neuropathy, optic neuropathy, hearing impairment) systems.<sup>20</sup> In this review, we have highlighted the neurotoxicity of Hg from a movement disorder perspective.

**Movement Disorders Associated with Mercury Exposure**

1. Named syndromic disorders:
  - (a) **Hunter Russell syndrome and Minamata disease:** In the early 1950s, an epidemiological study in Minamata, Japan first noticed that several cats fed on a fish diet were developing movement disorders, convulsions, and death (“dancing cat disease”).<sup>21</sup> In 1977, a similar incident was noted in Northwestern Ontario,

**Table 2: Historical vignettes of mercury exposure**

Country/region (Year/time)	Sources of exposure	Symptoms/effects
Cadiz, Spain (1810)	Accidental rupture of the bladders of two British ships (HMS Triumph and HMS Phipps) containing a huge quantity of rescued elemental Hg	Tremor, excessive salivation, dyspnea, tooth and skin problems, paralysis
California, USA (1848-early 1900)	California Gold Rush (USA) – the miners used around 10 million pounds of Hg at that time and most of it was released into the environment as tailings or mercury vapor	A century later, Sierra Nevada region of California still has a high concentration of Hg and MeHg in the water and soil, while the sediment-bound Hg has contaminated food webs of the San Francisco Bay Delta
Danbury, Connecticut, USA (in 19th and early 20th centuries)	Occupational exposure to Hg vapor affecting employees of hat factories, being exposed to Hg during the process of “carroting” and felting	Tremors (“Danbury shakes” or “the hatters’ shakes”) and behavioral issues (“mad hatter”)
Minamata and Niigata, Japan (1950s and ’60s)	Consumption of fish from contaminated water exposed to mercuric sulfate (metabolized to MeHg by bacteria in the sediment), being discharged into the sea and Agano River by industrial plants (Chisso Corporation in Minamata and Showa Denko Company in Niigata)	Hundreds of people died and thousands developed ataxia, dysarthria, sensory symptoms, spasmodic cramps, blindness, deafness, and paralysis
Pakistan (1960s)	Floor and wheat seed treated with Agrosan-GN containing ethylmercury chloride and phenylmercury acetate	Spastic paralysis, dysarthria, confusion, optic atrophy, spontaneous crying, involuntary sucking, or chewing movements
Guatemala (1960s)	Wheat seed treated with Panogen containing methylmercury dicyandiamide	Paralysis, blindness, deafness, rigidity, coma
Alamogordo, New Mexico, USA (1969)	Eating pork fed with floor sweeping of grain seeds, being treated with Panogen	Visual difficulty, ataxia, behavioral change, lethargy
Iraq (1970s)	“Wonder wheat” imported from Mexico, while seeds were being treated with cheap MeHg fungicide during shipment	More than 6500 people died and around 100,000 people developed tremor, ataxia and sensory symptoms
Poultney, Vermont, USA (1970s and ’80s)	Elemental Hg poisoning among workers at the Staco thermometer plant	Headaches, bleeding or sore gums, ataxia, upset digestive systems

Canada where cats were noted to develop ataxic gait, movement disorders, seizures, and uncontrolled howling.<sup>22</sup> Cerebellar ataxia, dysarthria, and visual field constriction constitute the classic triad of *Hunter-Russell syndrome* of organic Hg intoxication.<sup>23</sup> Postural and action tremor were prominent. Electrophysiological analysis of the postural tremor in Minamata disease and have noted the mean frequency of 7.1 Hz and mean amplitude of 1.8 mV.<sup>24</sup> Brain autopsy of patients with “Minamata disease” showed degeneration and damage to the calcarine region of the occipital lobe, central and temporal cortices, atrophy of the granular cell layer of cerebellum, and dorsal roots.<sup>25</sup>

- (b) **Danbury shakes:** In the 19th and early 20th centuries, workers of hat factories at Danbury, Connecticut, USA, exposed to Hg vapor during the process of “carroting” and felting, were noticed to have fine tremor in hands interrupted by coarse myoclonic jerks (“Danbury shakes”)<sup>26</sup> along with the behavioral issues ranging from pathological shyness to profound irritability, insomnia, hyperactivity and psychotic behaviors (“mad hatters”). Jerky postural tremor is one of the commonest presentations of elemental Hg poisoning and has been described in the literature as “mercurial tremors”, “metallic tremor” or “*tremblant metallique*”, the term used to describe the tremor noted in water gilders in Paris.

## 2. Other movement disorders

- (a) **Cerebellar ataxia and tremor:** Gait and limb ataxia, dysmetria, and dysdiadochokinesia along with

dysarthria and visual field constriction were reported in lamp socket manufacturers chronically exposed to elemental Hg.<sup>27</sup> Rhee et al. have reported subacute onset slowly progressive cerebellar ataxia from exposure to Hg vapor.<sup>28</sup> Subacute cerebellar ataxia has also been reported from the Indian subcontinent from ayurvedic medicine containing a high amount of Hg.<sup>29</sup> Malkani et al. have reported the development of limb and gait ataxia, dysdiadochokinesia, nystagmus, dysarthria along with multiple cranial nerve palsies from subcutaneous injection of elemental Hg (“quick silver pellets”) with the cultural belief of protection against sickness.<sup>30</sup>

A study in Brazilian gold traders exposed to Hg vapor have measured tremor frequency mainly in high-frequency windows (6.6–10.0 Hz).<sup>31</sup> Motor deficits in the form of tremor, incoordination and poor fine motor control, and subtle cognitive changes have been noted among dentists exposed to Hg.<sup>32</sup> A study by Rustam et al. on MeHg poisoning in Iraq, noted that around 13% of patients had intention tremor, while flapping and static tremor were less frequent.<sup>33</sup> Sequential neurological manifestations have been reported in Hg vapor (elemental mercury) poisoning. While initial symptoms can be upper limb weakness, intention tremor, loss of fine motor coordination, and numbness, continued exposure leads to coarser tremor and spasm interfering with feeding or writing. Tremor and spasm can later involve the lower extremity, trunk, and head.<sup>34</sup> Schaumburg et al. have reported the development of mild fine rapid rest tremor of the fingers, markedly exaggerated

**Table 3: Present global scenario of mercury exposure**

Major sources of exposure	Environmental impact and vulnerable population
Artisanal and small-scale gold mining (ASGM)	Mainly affecting rural communities of South American Amazon basin (e.g. in Peru, Ecuador, Suriname, Nicaragua, Columbia, Brazil), Asia (e.g. in Indonesia, Laos, Philippines, Mongolia), and Africa (e.g. in Burkina Faso, Guinea, Senegal, Ghana, Ivory Coast, Tanzania)
Stationary combustion of fossil fuel and biomass, specially coal-fired power plants	Coal combustion is the single highest contributor (around 50%) for atmospheric Hg emission in the USA. Mercury in the gaseous form is transported to Alaska year-round and around 20% of this mercury comes from Asia
Nonferrous metals production	Nonferrous metal (zinc, lead, and copper) smelting is one of the major sources of anthropogenic mercury emission (e.g. in China)
Cement production	Mercury is present in the raw materials (e.g. limestone) and/or in the fuel (e.g. coal) used in the cement manufacturing process
Aquatic ecosystem and marine food chain from the industrial mercury waste being dumped into the river system	Currently affecting residents of Grassy Narrows and White dog First Nations of Canada (Ontario Minamata disease), Aamjiwnaang First Nations community in southwest Ontario near Sarnia (Canada's "Chemical Valley")
Vinyl chloride monomer production	Highly volatile and toxic mercuric chloride catalyst is used in vinyl chloride monomer production (e.g. in China)
Chloralkali production	Though direct emissions to air and water from chloralkali plants in Western Europe and North America have decreased after they started using non-Hg cells, several tons of mercury is still being emitted every year in Western Europe causing human toxicity. Chloralkali products are also used for preparing food ingredients like high-fructose corn syrup
Use of dental amalgam	Amalgam fillings used by dentists in the recent past can emit mercury vapor which is highly volatile and lipid soluble and thus can cross the blood–brain barrier. By the weak acids present in food or while immersing the amalgam into sodium chloride solution, there occurs oxidative corrosion of amalgam and inorganic mercury is being released into the oral cavity
Alternative medicine use	Traditional Chinese, Tibetan, Ayurvedic, or Brazilian medicine using cinnabar (mercury sulfide, HgS) and calomel (mercurous chloride, Hg <sub>2</sub> Cl <sub>2</sub> ) for treatment of psoriasis, dermatitis, arthritis, sexually transmitted diseases, allergic rhinitis, and detoxification therapy
Skin-lightening cosmetic products	Often contain toxic mercury and are easily available by online shopping
Magico-ritualistic practices	Practitioners of Espiritismo, Santeria, and Voodoo – religious faiths prevalent in Afro-Caribbean and Latin American traditions use elemental mercury in magical spells for protection against evil spirits and to bring good luck
Subcutaneous injection of elemental mercury	Misused for suicidal attempts, tattoo augmentation, to ward off the evil spirits, to increase penile strength, and to increase athletic ability
Mishandling or improper disposal of Compact Fluorescent Lamps (CFLs), thermometers, thermostats, batteries, and some temperature or pressure sensitive switches	
Others: biomass burning, waste incineration, oil refining, cremation	

on movement, in a patient with a history of self-administration of elemental mercury subcutaneously.<sup>35</sup> Bradberry et al. have reported a case of a 36-year-old jewelry producer exposed to Hg vapor presenting with a coarse tremor of the hands and protruded tongue, slurred speech, cerebellar ataxia, and constricted visual fields.<sup>36</sup>

- (b) **Myoclonus:** Roullet et al. have reported severe intention and action myoclonus in a 58-year-old laboratory glassware manufacturer with occupational exposure to Hg vapor.<sup>37</sup> Ragothaman et al. have described a case of a 23-year Chemistry graduate, who developed progressive generalized myoclonus and ataxia as a result of self-injecting elemental mercury.<sup>38</sup> Myoclonus was present at rest and worsened with activity. Electrophysiological studies revealed large-amplitude (12.1  $\mu$ V) somatosensory-evoked potential (SSEP) and high frequency (10–30 Hz), short duration (less than 50 ms) EMG bursts, suggesting the cortical origin of the myoclonus. The symptoms improved after surgical clearance of the subcutaneous Hg deposits from the injection site.
- (c) **Chorea:** Ko et al. have reported the development of generalized chorea from Hg poisoning in a 50-year-old female, in whom symptoms improved with chelation

therapy.<sup>39</sup> Chorea, athetosis, and hemiballismus were reported in patients exposed to MeHg in Japan and Iraq.<sup>33,40–42</sup>

- (d) **Parkinsonism:** Hsu et al. noted that in patients exposed to dental amalgam fillings, the incidence of PD was 1.5 times higher than those nonexposed.<sup>43</sup> Some studies have also noted a higher incidence of PD in dentists when regularly exposed to Hg vapor.<sup>44,45</sup> Finkelstein et al. reported the development of hemiparkinsonism in a 47-year-old female dentist who improved with chelation therapy by D-Penicillamine.<sup>46</sup> Fabrizio et al. have noted a high prevalence of extrapyramidal signs and symptoms (PD, postural tremor) in a group of male dental technicians working in a technical high school in Rome.<sup>47</sup> Miller et al. have reported a case of a 55-year-old worker of chlorine factory, who developed parkinsonism after chronic exposure to metallic Hg vapor.<sup>48</sup> Palacios et al. have investigated a possible correlation between airborne metal exposure of female nurses and risk of PD by a large prospective study with a study duration of 18 years (1990–2008) and involving 121,701 participants from 11 different US states.<sup>49</sup> In the study, Hg was the only metal found to be associated



with the highest risk of PD (CI = 0.99–1.79). A study by Dantzig<sup>50</sup> has also shown the possible relation between PD and chronic low levels of Hg poisoning in susceptible individuals.<sup>50</sup> The study noted that detectable blood Hg levels were six times more frequent in individuals with PD than in healthy controls and proposed that a dermatological manifestation of chronic Hg exposure, Grover's disease (transient acantholytic dermatitis), may be a clinical clue to predict who are at risk of developing PD. Lin et al. showed a significant decrease in striatal dopamine transporter (DAT) in workers exposed to Hg vapor.<sup>51</sup> However, unless a definite correlation between chronic Hg exposure and development of PD is shown in large-scale human studies, the possible link between Hg and PD remains a matter of debate.

### 3. Mercury and autoimmune movement disorders

Recently, Pérez et al. have summarized 41 cases of Hg-induced Morvan syndrome, the autoimmune disorder related to antibodies against contactin-associated protein-like 2 (Caspr2).<sup>52</sup> Features of peripheral nerve hyperexcitability like neuromyotonia, electromyographic evidence of myokymia along with encephalopathy, insomnia, and autonomic dysfunction are the hallmarks of Morvan syndrome. Additional painful paresthesia, severe myalgia, arthralgia, and generalized rash were noted by Pérez et al. in "Morvan syndrome-plus" related to an accidental indoor spill of metallic Hg. In addition to the characteristic anti-Caspr2 antibody, other antibodies like anti-leucine-rich glioma-inactivated protein 1 (LGI1), anti-glutamic acid decarboxylase 65-kilodalton isoform (GAD65), and anti-voltage-gated calcium channel (VGCC) antibodies were detected by Pérez et al., suggesting larger spectrum of autoimmune response to Hg. In the literature, varied source of exposure to Hg and resulting Morvan syndrome-like phenotype with serum anti-Caspr2 positivity has been described. Like accidental spillage of a bottle of Hg beads, therapeutic use of mercuric iodide, use of skin whitener, and taking indigenous or ayurvedic medicine.<sup>53–57</sup> Similarly, Malkani et al. noted anti-Purkinje cell cytoplasmic-type Tr antibody positivity in a case of elemental mercury toxicity presenting with cerebellar ataxia.<sup>30</sup> In a developing country like India, ayurvedic drugs containing Hg are still being used abundantly and the physician should never forget to take detailed drug history when a patient presents with such phenotype.

### 4. Other neurological features associated with mercury-induced movement disorders

Some neurological features apart from movement disorders are often associated with elementary and organic Hg exposure and can be vital clues for the clinicians to suspect this toxic etiology. Neuropsychiatric symptoms of chronic elementary Hg exposure can range from irritability, insomnia, excessive dreaming to the full-blown picture of "erythrism" in the late stage with personality changes, excessive shyness mixed with nervousness and irritability, anxiety, depression, delirium, hallucination, and seizures.<sup>58,59</sup> Dyspnoea, hypersalivation, skin ulceration, and tooth loss are other clues that can indicate elemental Hg poisoning.

On the other hand, moderate to severe constriction of the bilateral visual fields is one of the characteristic features of MeHg poisoning along with sensory impairment in distal extremities in the form of paresthesia and numbness.<sup>60</sup> Perioral sensory disturbance with an "onion peel" somatosensory distribution can be seen.<sup>61,62</sup> Hearing difficulty, dizziness, and unsteadiness are commonly associated.<sup>63,64</sup>

## Management of Suspected Mercury Exposure/Toxicity

### Laboratory Investigations

Detailed history including occupational exposure and thorough clinical examination still hold the key in diagnosing Hg-related movement disorders. Any exposure to indigenous or ayurvedic medicine and any practice of magico-ritualistic use of Hg should not be overlooked either. Laboratory investigations to detect the presence of Hg intoxication include blood and urine Hg levels, assays on scalp hair and toenail samples.<sup>65</sup> A literature review by Fields et al., comprising over 3000 workers chronically exposed to elemental Hg, has mentioned that physical examination (tremor, incoordination, brisk reflexes) is more important for assessing workers with urinary Hg level > 200 µg/L, while for those with low urine Hg levels, neurobehavioral testing is more useful.<sup>66</sup> However, the slow excretion of Hg from the body and non-accuracy to predict the timing of neuronal injury make these assays not very helpful in Hg-induced neurotoxicity. Lack of adequate dose–response studies makes it difficult to set a threshold level for Hg in blood or urine for immunologically sensitive individuals.

### Chelation Therapy

D-Penicillamine has been used as an oral chelating agent in inorganic Hg toxicity (adult dose: 250 mg qid, pediatric dose: 20–30 mg/kg/day for 1–2 weeks), but has no role in MeHg exposure.<sup>67,68</sup> Hypersensitivity and nephrotoxicity are the commonest side effects of penicillamine. Similarly, dimercaprol or British anti-Lewisite (BAL) has also been used successfully mainly in inorganic and elemental mercury poisoning (deep intramuscular injection of 5 mg/kg for every 4 h for 1–2 days, then 2.5 mg/kg one–two times/day for 10 days).<sup>29,69</sup> Nausea, vomiting, hypertension, tachycardia, headache, diaphoresis, and convulsions are the common side effects of dimercaprol.

The water-soluble analogues of BAL, 2,3-dimercaptopropane sulfonic acid (DMPS), and Meso 2,3-dimercaptosuccinic acid (DMSA) are better alternatives for detoxification in elemental or organic Hg exposure.<sup>70</sup> They can be administered orally or as an IV injection. In the Mt. Diwata study (Philippines), gold miners exposed to elemental mercury were compared to people living downstream who were exposed to MeHg from eating fish and to controls without known exposure to Hg.<sup>71</sup> One-hundred and six probands completed the 2-week trial of oral DMPS 400 mg daily. The study noted a marked improvement in hypomimia, pencil tapping, Romberg test, tremor, and ataxia. Importantly, the therapeutic efficacy was almost similar between the participants exposed to the elemental mercury group (miners) and in the MeHg group (downstream fish eaters). In another study, among patients with occupational exposure to Hg vapor, 2 weeks of oral

DMPS 100 mg thrice daily followed by DMPS 100 mg four times a day for an additional 6 weeks have shown beneficial effects.<sup>72</sup> Dose of DMSA is 10 mg/kg (350 mg/m<sup>2</sup> in children) tid for the initial 5 days, followed by 10 mg/kg (350 mg/m<sup>2</sup> in children) bid for the next 14 days.<sup>1</sup> Newer DMSA analogues like Mono isoamyl ester of DMSA (MiADMSA), Monomethyl DMSA (MmDMSA), and Monocyclohexyl DMSA (MchDMSA), either alone or in combination with DMSA, are also being studied for better chelation therapy.<sup>73</sup>

### Preventive Measures for Mercury Contamination

Though the overall Hg emissions into the environment have decreased over the past decades, improper disposal of industrial waste, artisanal gold mining, and indiscriminate use and more importantly disposal of Hg-containing products like dental amalgam, CFLs, batteries, etc., are still polluting our ecosystem and affecting us via different routes. Minamata Convention on Mercury, a global treaty, has been formed to address these issues. Different preventive measures can be taken to minimize the Hg contamination like: (i) maintaining proper protocol for transport and handling of Hg products; (ii) installation of ISO-11143-certified amalgam separators; (iii) using Hg-free dental materials; (iv) using carbon nanotubes (CNTs) to remove Hg from water; (v) operationalizing proper collection and recycling programs for Hg-containing lamps; (vi) stopping the use of Hg cells in chloralkali plants and upgrading them to newer “membrane technology”; (vii) substitution by non-Hg alternatives in residential or industrial sectors; (viii) restricting the use of Hg in gold mining and using other techniques like “concentration methods”, “direct smelting”, or “cyanide leaching” to extract gold; (ix) controlling Hg emissions through “end-of-pipe techniques” like exhaust gas filtering and using controlled landfill for waste disposal; (x) proper vigilance on the misuse of Hg in indigenous medicine available in the market or online; and (xi) prohibition of the misuse of Hg in magico-ritualistic practices.<sup>1,74–77</sup> The measures need to be strictly implemented and monitored. More active involvement of the groups such as the United Nations Environment Programme or the Artisanal Gold Council is needed to teach the miners to incorporate relatively inexpensive technologies into their work so that they can sustain their livelihood and perhaps enjoy a better life with less exposure to Hg.<sup>78</sup> Finally, trading in hazardous wastes like ship breaking industry, though provides raw materials as an incentive to the weaker economy of developing countries, also adds to toxic wastes that have serious implications on environmental and human health. Though the 1989 Basel convention seeks to halt such transport of hazardous wastes, illegal trade and exports between less regulated countries persist.<sup>79</sup> There should be means to recycle or reuse this waste to prevent toxic exposure to the native population and workers.

### CONCLUSION

Toxic effects of Hg have affected humanity through the pages of history. Modernization of society has changed modes of human exposure, but Hg is still a potential etiology in patients presenting with cerebellar ataxia, postural and action tremor, myoclonus or myoclonus ataxia, parkinsonism, and autoimmune movement disorders. With a wide range of neurological symptoms, clinicians should be well aware of the toxic profile of Hg

and detailed occupational, environmental, and drug history should always be taken.

Chelation with DMPS or its analogues has shown efficacy as therapeutic agents for Hg toxicity but more clinical trials are needed. Unfortunately, irreversible neuronal damage often already sets in by the time neurological signs manifest, thus chelation therapy may be ineffective. Thus, it is of utmost importance to eliminate the potential dietary or occupational source to prevent neurodegeneration. Finally, implementation and monitoring of strict regulatory guidelines and strategies to combat environmental Hg toxicity are indispensable to prevent its neurotoxicity and protect our beautiful world.

### TAKE HOME MESSAGE

1. Human exposure to Hg is still prevalent in the modern world.
2. Cerebellar ataxia, tremor, and myoclonus are common movement disorders from exposure to Hg.
3. Parkinsonism and autoimmune Morvan syndrome can be associated with Hg.
4. Detailed occupational, environmental, and drug history are the keys to diagnose Hg-induced movement disorders.
5. Preventive strategies must be implemented globally to get rid of the toxic effects of Hg.

### CONFLICT OF INTEREST

No authors have any conflict of interest to disclose.

### STATEMENT OF AUTHORSHIP

1. Research project: A. Conception, B. Organization, C. Execution.

2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

JG: 1B, 1C, 2A.

DK: 1B, 1C.

MJ: 1A, 2B.

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