Neurologic Complications of Medical Disease
C63, April 24, 2017 7.00 am – 9.00 am
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CNS Toxicities: Metals
4/24/2017, 8.30 am – 9.00 am
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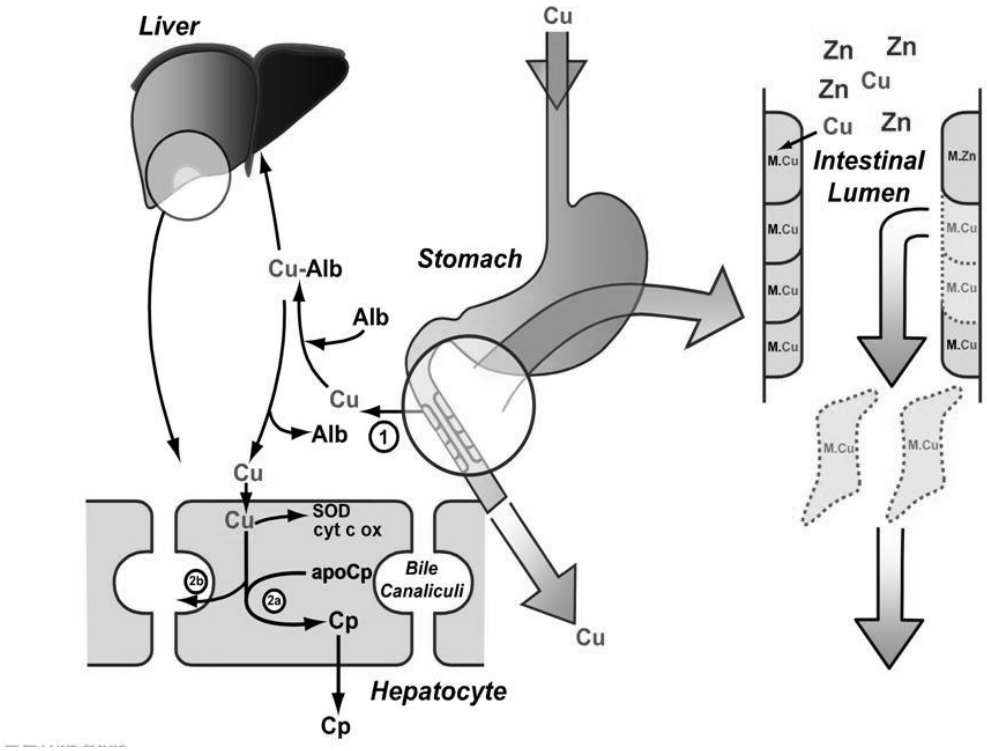
Zinc Induced Copper Deficiency and Neurologic disease

- ***Mechanism of zinc induced copper deficiency***
  - Excess zinc ingestion is a well-recognized cause of copper deficiency. Zinc causes an upregulation of metallothionein production in the enterocytes. Metallothionein is an intracellular ligand and copper has a higher affinity for metallothionein than zinc. Copper displaces zinc from metallothionein, binds preferentially to the metallothionein, remains in the enterocytes, and is lost in the stools as the intestinal cells are sloughed off.
- ***Hematologic manifestations of copper deficiency***
  - Hematological manifestations of copper deficiency are well recognized and include anemia and neutropenia. Typical bone marrow findings include a left shift in granulocytic and erythroid maturation with cytoplasmic vacuolization in erythroid and myeloid precursors and the presence of ringed sideroblasts.
- ***Neurologic manifestations of copper deficiency***
  - Copper deficiency-associated myelopathy has been well described in various animal species. Often seen in ruminants, it has been called swayback or enzootic ataxia.
  - Neurologic manifestations of acquired copper deficiency in humans have been increasingly recognized over the past decade.[1-4] Copper deficiency results in a myeloneuropathy that resembles the subacute combined degeneration seen with vitamin B_{12} deficiency. Neuroimaging may show an increased T2 signal involving the dorsal column.
- ***Potential sources of zinc exposure***
  - In addition to the common use of zinc in the prevention or treatment of common colds and sinusitis, zinc therapy has been used, often empirically, for conditions like acrodermatitis enteropathica, decubitus ulcers, sickle cell disease, celiac disease, glucagonoma, hepatic encephalopathy, psychosis, memory impairment, diarrhea, myoclonic epilepsy, and acne.
  - Unusual sources of excess zinc have included patients who used excessive amounts of zinc containing denture cream for long periods.[5, 6] and patients swallowing zinc containing coins.[7] Excess use of zinc containing denture creams has been implicated in patients with zinc-induced copper deficiency-related myeloneuropathy.[5, 6] A recent report suggests that patients with hyperzincemia of unknown cause and copper deficiency myeloneuropathy may have had denture cream use as a possible source that was not specifically looked for.[6] In this report the use of denture fixatives in 11 patients with myeloneuropathy – hypocupremia – hyperzincemia was evaluated and the study noted a history of poorly fitting dentures and application of excessive amounts of denture adhesives in all. Individual susceptibility may play a role in hyperzincemia induced hypocupremia and related neurologic manifestations.
- ***Zinc induced copper deficiency in Wilson disease***
  - Copper accumulation in the liver and brain underlies the pathophysiology of Wilson disease. Zinc decreases copper absorption and over the years has assumed an increasingly important role in the management of WD. Chronically administered high doses of oral zinc have been used in patients with WD, generally without the development of neurological complications. In some recent reports over treatment of WD with zinc has been accompanied by neurologic manifestations related to zinc excess/ copper deficiency.[8, 9]
- ***Note:*** Copper is absorbed in the stomach and proximal small intestine. An additional risk factor for copper deficiency is copper deficiency secondary to gastric surgery. The presence of multiple causes can increase the chances of development of a clinically significant deficiency state.

Figure:

Zinc toxicity and copper deficiency: Excretion of copper into the gastrointestinal tract is the major pathway that regulates copper homeostasis and prevents deficiency or toxicity. Excessive zinc ingestion is a well recognized cause of copper deficiency. The zinc-induced inhibition of copper absorption could be the result of competition for a common transporter or a consequence of induction of metallothionein in enterocytes. Metallothionein has a higher binding affinity for copper than for zinc. Copper is retained within the enterocytes and lost as the intestinal cells are sloughed off. Failure to mobilize absorbed copper from intestinal cells forms the basis of Menkes disease (1). In Wilson disease there is decreased incorporation of copper into ceruloplasmin (2a) and impaired biliary excretion of copper (2b).
Abbreviations-Cu: copper, Zn: zinc, Cp: ceruloplasmin, M: metallothionein, alb: albumin, SOD: superoxide dismutase, cyt c ox: cytochrome c oxidase, WD: Wilson disease, MD: Menkes disease.



Neuropathy Due to Cobalt-Chromium Metallosis after Hip Replacement

- Total hip arthroplasty may be complicated by corrosion and disassembly of the components. Metallosis is a very rare complication of arthroplasty. It refers to chronic infiltration of metallic wear debris into the periprosthetic bony and soft tissues.[10] Reactive chronic inflammatory changes are seen. Wear debris can rarely cause systemic intoxication by prosthetic metallic materials, mostly by cobalt-chromium.
- ***Neurologic complications of metallosis***
    - Neurologic complications of metallosis are restricted to a few case reports and include peripheral neuropathy, at times associated with impaired vision, hearing, or both.[11-14] Cobalt and chromium levels are elevated. Hypothyroidism or cardiomyopathy may be present.[13, 14]
    - Improvement in neurologic manifestations results from revision surgery and removal of prosthetic component. Chelation has been reported to reduce metal levels but not improve neurologic manifestations.[12]
    - A recent report described detailed analysis of the peripheral neuropathy seen in a patient with metallosis after hip arthroplasty with a cobalt-chromium alloy prosthesis.[13] The neuropathy was painful, distally prominent, and accompanied by impaired distal position perception, absent deep tendon reflexes, and slight distal weakness. Bilateral sensorineural hearing impairment was present. Sensory nerve action potentials were absent. Motor conduction studies were normal. The patient had marked elevations of blood cobalt and chromium. A sural nerve biopsy showed moderate axonal degeneration without significant inflammation. The authors speculate that absence of inflammation may have been related to the low dose prednisone that the patient was on. Cobalt and chromium levels

in the sural nerve were increased compared to controls. X-ray of the hip showed a deformity in the cobalt-chromium head of the prosthesis. During surgery, the metallosis was found to have spread from the right hip joint to the thigh. Revision arthroplasty and removal of soft tissue contaminated with metal debris was accompanied by gradual clinical and electrophysiologic improvement, and decrease in blood levels of cobalt and chromium.

- Though very rare, this topic has gained a lot of attention in recent years. Total hip arthroplasty is a commonly done and well established surgical procedure.

Gadolinium and Nephrogenic Systemic Fibrosis

- Gadolinium is a lanthanide metal with paramagnetic properties that make it an excellent contrast agent to improve the utility of MRI. Two complications related to use of gadolinium-based contrast agents have been recognized (both in patients with underlying renal disease): nephrotoxicity and nephrogenic systemic fibrosis.[15]
- ***Nephrogenic Systemic Fibrosis***
  - The disease was initially referred to as a "scleromyxedema-like disorder of renal dialysis patients", then as "nephrogenic fibrosing dermopathy". Recognition that fibrosis also occurred in systemic organs led to the name "nephrogenic systemic fibrosis". Progressive dural calcification, thickening, and enhancement may be seen.[16]
  - Recognition that nephrogenic systemic fibrosis developed in patients with end stage renal disease and exposure to gadodiamide led to identification of the underlying etiology.[17]
  - High doses and large cumulative doses are associated with increased risk. The highest risk is in patients with ESRD, stage 5 CKD, and AKI. Gadodiamide is associated with a higher risk than gadopentetate. The macrocyclic chelate gadoteridol has the least risk.
  - Symptoms usually begin within 2 months after exposure to gadolinium-based contrast and include severe pain, burning, and tightening of the skin with associated redness and swelling. This evolves into joint contractures and immobility.
  - Gadolinium-based contrast agents should be avoided with a GFR <30ml/mt and are contraindicated in patients on dialysis.[18]

- ***Pseudoneurotoxic disease*** [19-21]

Type	Features	Example
Type I	A naturally occurring nervous system disease or condition is attributed to coincident chemical exposure	A welder with PD is incorrectly diagnosed as having Mn neurotoxicity because of concerns regarding occupational exposure
Type 2	An acquired psychogenic disorder, seemingly precipitated by exposure to trivial amounts of a neurotoxicant	A patient with anxiety related concentration difficulty that is incorrectly attributed to potential environmental exposure to Pb when in was in an older home with peeling paint
Type 3	A pre-existing neurologic or psychologic condition is felt to be worsened or altered following exposure to an exogenous agent even though the agent is not associated with the pre-existing condition	A chronic daily headache that develops in a migraineur after being in an area that had a Hg spill from a broken thermometer

- ***General principles of neurotoxicology with examples of metal that highlight the stated principle*** [22]

General Principle	Example
Brief latent period between exposure and clinical manifestation	Pb encephalopathy
Physiologic variables like age may dictate clinical presentation	Unlike adults, in children the CNS is more vulnerable to Pb toxicity than the PNS
Chemical state of the toxin dictates clinical manifestations of toxicity	Hg
Slight changes in chemical structure significantly	Organic arsenicals are nontoxic

impacts toxicity	
Implicated agent is considered innocuous until it is reported to cause human disease.	Neurotoxicity of a metals like arsenic became evident in the setting of its therapeutic use for various ailments
Deterioration may continue for weeks despite removal from the toxic source ("coasting").	Toxicity due to platinum based drugs
Significant recovery occurs following termination of acute exposure.	Pb
Neurologic manifestations associated with acute high-level exposure are different from that seen with prolonged low-level exposure	The asymmetric neuropathy with upper limb involvement is seen following subacute exposure to high levels of Pb, chronic lower level exposure may result in a sensorimotor neuropathy
Clinical deficits are generally symmetric	Metal neuropathy is generally symmetric (exception pallidal toxicity with manganese)
Selective vulnerability	Hg affects the dorsal root ganglion and cerebellum but spares the anterior horn cell
More than one neurological syndrome may result from the same toxin	Mn may cause neurobehavioral sequelae or an extrapyramidal disorder
Same neurological manifestation may result from different toxins	*Arsenic and thallium can cause a GBS like neuropathy*
Uncertain impact of chronic, low-level, long term exposure	Manganese
Characteristics signs may suggest a specific disorder	Alopecia with thallium toxicity

- ***Arsenic***[20, 21]

Historical	• Fowler solution (potassium arsenite) was used as a medicinal agent until 1950s
Forms	• Elemental: nontoxic • Inorganic: trivalent (arsenite) and pentavalent (arsenate); arsenite is more toxic • Organic: arsenobetaine (seafood, nontoxic) • Arsine gas (AsH_3)
Use/ Source/ Exposure	• Smelting, mining, abrasive blasting • Hardening lead in battery grids, bearings, cable sheaths • Furnace and flue maintenance operations, fly ash from coal broilers, burning As treated wood (CCA is a wood preservative) or agricultural waste • Pesticide manufacturers and applicators, forestry and farm workers • Herbicides and desiccants in cotton harvesting and in sheep and cattle dips • Microelectrionics and semiconductor industry • Glass, ceramic, pigment making industry, in the electrolytic production of zinc • Well water, dried milk, soy sauce, moonshine • Intentional poisonings • Smoking treated tobacco, drinking wine made from treated grapes • Herbal products, Arsanilic acid in veterinary pharmaceuticals and feed additives • Preservatives in tanning and taxidermy • As_2O_3 in Rx of acute promyelocytic leukemia, melarsoprol in Rx of trypanosomiasis
Kinetics	• Absorbed after ingestion, inhalation (occupational exposure), skin contact • Pentavalent As and arsine are converted to the trivalent form in vivo • As rapidly disappears into body pool of phosphates • As body burden in skin, hair, nails, bone, teeth • Trivalent As is methylated and excreted in urine
Mechanism of action	• Trivalent As binds to -SH groups & interferes with enzyme activity, protein synthesis, and DNA repair • Uncouples oxidative phosphorylation and interferes with gluconeogenesis
Clinical	• Acute: Gastrointestinal illness followed by encephalopathy. Others: multiorgan failure,

	ascending PN that mimics GBS, metallic taste, garlic odor • Chronic: PN, skin changes, Mees' lines, alopecia, portal hypertension, bone marrow suppression, pulmonary disease, gastrointestinal disturbance, "blackfoot disease" • Carcinogen • Arsine gas: abdominal pain, hematuria, jaundice
Laboratory	• Anemia, pancytopenia, basophilic stippling, ↑ hepatic transaminases, renal • Patchy infiltrates on abdominal radiographs due to metal • ECG changes • Blood arsenic levels are of limited utility, because serum arsenic is cleared within hrs • Urinary As analysis is most frequently used to assess chronic toxicity and to monitor occupational exposure (Care: increased due to nontoxic organic forms in seafood) • Limited utility of hair and nail arsenic, chelation challenge • NCS/ EMG: demyelinating polyradiculoneuropathy followed by distal axonopathy
Prevention	• Engineering control, personal protective equipment, medical surveillance, biologic monitoring of urine As, precautions with CCA-treated wood
Management	• Emesis, activated charcoal, cathartic • DMPS, DMSA, penicillamine, BAL • Arsine: alkaline diuresis, exchange transfusion, hemodialysis (no role for BAL)
Additional comments	• As_2O_3 is used in the treatment of promyelocytic leukemia • Melarsoprol is used in the management of trypanosomiasis

- ***Lead***[20, 21]

Historical	• Pb neuropathy in epidemic proportions during industrial revolution
Forms	• Elemental or metallic • Inorganic • Organic
Use/ Source/ Exposure	• Release into the environment from automobile and industrial emissions, Pb-based paints, incineration of waste containing Pb additives, burning of coal, crushing and smelting of Pb and other metal ores, blasting and sanding of Pb coated surfaces • Welders exposed to Pb alloys, fluxes, coatings • Pb stabilizers in plastics • Monnshine whiskey, acidic beverages in improperly fired ceramic glasses • Herbal remedies, gasoline sniffing, water in Pb pipes • Ammunition, batteries, cable sheaths, ceramics, glazed pottery, cosmetics, costume jewelry, crystal, crayon and art supplies, pottery, stained glass, solder, herbal medications, plastics, paints and pigments, solder, and candle wicks • Sheet Pb: Radioactive shielding, waterproofing, soundproofing, line chemical reaction vessels • Antiknock agents in gasoline (tetraethyl and tetramethyl Pb) (some parts of the world)
Kinetics	• Inhalation and ingestion, alkyl lead compounds are absorbed through skin also • Tetraethyl and tetramethyl Pb are converted into toxic, lipid soluble, trialkyl metabolites and then into inorganic Pb which is excreted in urine • GI absorption is greater in children and is increased by iron/ calcium deficiency • Majority of absorbed lead is bound to RBCs, free plasma fraction is distributed to brain, liver, skin, skeletal muscle, and is renally excreted • Fetal levels correlate with maternal levels • Bone is the major site of deposition of absorbed Pb, $t_{1/2}$ of stored lead is 5-10 years • Increased mobilization of stored lead with aging, osteoporosis, fractures, pregnancy, lactation, menopause, hyperthyroidism
Mechanism of action	• Binds to –SH groups, interferes with enzymes (including heme synthesis) • Binds to mitochondrial membranes and interferes with protein synthesis • Ability to interfere with the regulatory action of calcium in cell systems may lead to its effect on voltage-gated channels and synaptic transmission.
Clinical	• Acute or subacute: colicky abdominal pain, encephalopathy, renal failure, asymmetric motor PN

	with upper limb involvement (Differential diagnosis: ALS) • Chronic: fatigue, insomnia, neurobehavioral symptoms, PN, constipation, colicky abdominal pain, gout, hypertension, gingival lead line, renal insufficiency
Laboratory	• Anemia, basophilic stippling, reticulocytosis, hemolysis, leukopenia • Blood Pb level (screening), free RBC protoporphyrin (chronic), Zn protoporphyrin • Ur coproporphyrin & aminolevulinic acid; Aminoaciduria, glycosuria, phosphaturia • Elevated creatinine, BUN, uric acid, liver enzymes • Limited utility of hair and nail arsenic, chelation challenge • Abdominal radiographs may show paint chips, lead lines of bone growth arrest • NCS • K-band x-ray fluorescence of bone
Prevention	• Workplace hygiene: showering and cleaning of work garments • Removal from exposure in workers with average lead level over 50 μg/dl
Management	• Emesis, catharsis, endoscopic removal, hydration • $CaNa_2EDTA$, DMSA, BAL • Chelation of no benefit in alkyl lead intoxication
Additional comments	• Definite threshold below which no adverse effects will occur has not been established

- ***Therapy of lead poisoning***[20, 23]

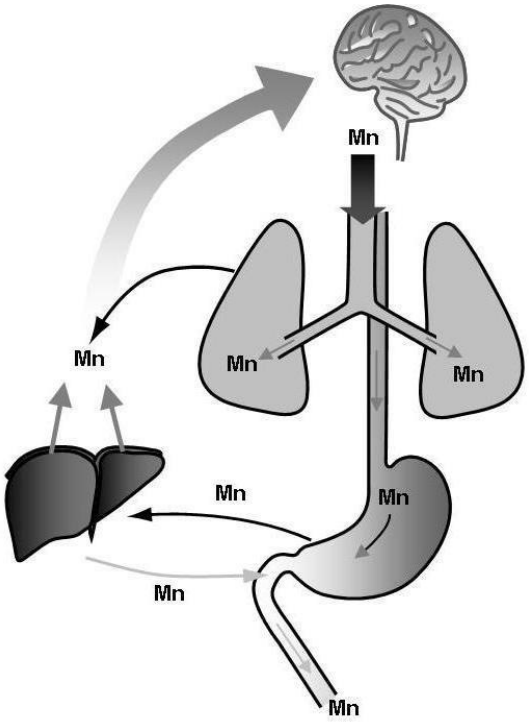
Lead encephalopathy	• BAL 25 mg/kg/day IM divided into six doses for 3 to 5 days • $CaNa_2EDTA$ 30 to 50 mg/kg/day as a continuous infusion starting 4 hours after initial BAL dose for 5 days (may be given IM in 2 or 3 divided doses if there is a need for volume restriction) Note: BAL pretreatment may prevent encephalopathy • Decide regarding need for an additional course based on lead concentrations after a 2 day rest and presence of symptoms • A third course may be required if blood lead concentrations rebound to 50 μg/dl or greater within 2 days after second course • If a third course is required it should start 1 week after last dose of BAL and $CaNa_2EDTA$
Symptomatic lead poisoning without lead encephalopathy	• BAL 2 to 3 mg/kg IM every 4 hours • $CaNa_2EDTA$ 20 to 30 mg/kg /day as a continuous infusion starting 4 hours after initial BAL dose for 5 days • BAL may be discontinued when blood lead concentrations decrease to less than 50 μg/dl but $CaNa_2EDTA$ treatment should continue for 5 days with need for additional courses being decided by blood lead concentrations • May convert to an oral chelating agent like succimer
Asymptomatic patients with high lead concentrations (adults: 70 to 100 μg/dl, children: 45 to 70 μg/dl)	• Succimer 10 mg/kg PO every 8 hours for 5 days followed by 10 mg/kg PO every 12 hours for 14 days Or • Two 5 day courses of the higher dose succimer therapy separated by a week[24] Or • $CaNa_2EDTA$ 25 mg/kg/day as continuous slow IV infusion or every 8 to 12 hours for 5 days Note: Decide on need for repeat treatment after 10 to 14 days period of reequilibration

- ***Manganese***[20, 21]

Historical	• Initial reports in manganese miners

Forms	• Elemental: metallic manganese (ferroMn in steel production) • Inorganic: Manganese dioxide (batteries, firework), manganese chloride (animal feed), manganese sulfate (fertilized), potassium permanganate (water purification) • Organic: (fungicides, antiknock agent)
Use/ Source/ Exposure	• Miners, smelting plant workers, manganese ore crushing plants, welders • Batteries, ceramics, coloring glass, enamel, electronics, fertilizers, fungicides (maneb and mancozeb), fragrances, flavorings, fireworks, gasoline additive, linoleum, paint, soap, steel alloys, and varnish • Patients with liver disease and portosystemic shunts • TPN • Potassium permanganate: enteral poisoning, psychostimulant • Mn is an essential trace element • Mn containing foods: nuts, grains, tea, lefumes
Kinetics	• Mn enters body via ingestion or inhalation • Mn absorption increases in Fe deficiency • Majority of ingested Mn is excreted in feces • Absorbed Mn is excreted via biliary excretion (a small amount in the urine) • Mn readily crosses the BBB and is concentrated in the striatum
Mechanism of action	• Proposed mechanisms of manganese neurotoxicity include oxidative stress generated through mitochondrial perturbation, N-methyl-D-aspartate mediated excitotoxicity, and disruption in iron metabolism
Clinical	• Acute toxic exposure is associated with pulmonary symptoms and nonspecific complaints • Cognitive disturbance ("manganese madness"): emotional instability, compulsive behavior, spontaneous laughter or crying, frank psychosis • Extrapyramidal syndrome: symmetrical disorder with an action-postural tremor (rather than rest tremor), dystonia, early gait difficulties including "cock walk gait), and behavioral manifestations • In cirrhotics, the extra-pyramidal syndrome may be seen without hepatic encephalopathy • Hepatic myelopathy: spastic paraparesis with paucity of sphincteric or sensory disturbance
Laboratory	• MRI: increased T1 signal on MRI • Limited utility of urine Mn and chelation challenge • Blood Mn can be detected for days after exposure
Prevention	• Adequate ventilation, protective devices • Amount of Mn in TPN
Management	• $CaNa_2EDTA$ • Limited l-dopa responsiveness
Additional comments	• Relationship between welding and PD-Parkinsonism is controversial

- ***Manganese kinetics*****:** Manganese enters the body by ingestion or inhalation. In the gastrointestinal tract manganese utilizes the same carrier as iron. Its absorption is therefore increased during states of iron deficiency. Only 2-5% of ingested manganese is absorbed. It enters the portal blood and is eliminated almost exclusively by the liver via biliary excretion. If the hepatic excretion mechanism is overwhelmed, manganese accumulates in the body. Excess blood manganese crosses the blood brain barrier and is selectively concentrated within the striatum. [21]



- ***Manganese neurotoxicity***[21, 25]

Neurobehavioral	Irritability, impulsiveness, aggression, belligerence, obsessive compulsive behaviors, hallucinations (visual and auditory), pseudobulbar affect with emotional incontinence, frank psychosis
Distribution of motor manifestations	Bilaterally symmetrical (simultaneous in onset)
Involuntary movements	Low amplitude action-postural tremor which may disappear as other deficits progress (usually no rest tremor, tongue tremor reported), action myoclonus, dystonia (limbs: foot dystonia and dystonic gait, trunk, face: dystonic smile)
Gait	Early appearance of gait and balance abnormalities with difficulty walking backwards, freezing during turns, retropulsion and propulsion, "cock-like" gait (strutting on toes with arms flexes and spine extended)
Speech	Early appearance of hypokinetic-hypophonic dysarthria
Pyramidal signs	Hyperreflexia and extensor plantar response
Response to levodopa	Poor or no sustained response to levodopa (no levodopa related motor or psychiatric manifestations)
Course	Initial rapid progression followed by stability or partial improvement or continued worsening (The extrapyramidal syndrome may progress over years even after removal from the source of toxicity)
Laboratory investigations	Initial and transient elevation of manganese in blood, urine, and hair
MRI	Bilateral hyperintensities in globus pallidus and substantia nigra on T1-weighted images (may be transient)
F-DOPA PET	Usually normal (sparing of the nigrostriatal system)
Pathology	Degeneration and gliosis of globus pallidus (and to a lesser extent striatum), no Lewy bodies

- ***Differences between manganese-induced parkinsonism and Parkinson disease***[21]

	Manganese-induced parkinsonism	**Parkinson disease**
Symmetry	Yes	No

Tremor	Action-Postural	Rest
Dystonia	Early and prominent	Less common
Gait difficulties	Early	Late
Neurobehavioral manifestations	Early	Late
FD-PET	Normal	Decreased uptake in posterior putamen
MRI	Increased pallidal signal on T1-weighted images	Normal
Site of pathology	Pallidum and striatum (no Lewy bodies)	Substantia nigra pars compacta (nigral degeneration and Lewy bodies)
Response to levodopa	Absent or transient, no levodopa induced motor complications	Present

- ***Mercury***[20, 21]

Historical	• Felt industry in 19th century, Minamata bay incident in Japan, poisoning in Iraq due to eating grain contaminated by organic mercury containing fungicides
Forms	• Elemental or metallic: vapor or liquid (dental amalgam and thermometers) • Inorganic salts or minerals (industrial toxin, not environmental pollutant) • Organic (methyl mercury in sea food)
Use/ Source/ Exposure	• Released into atmosphere from volcanoes and industrial emissions • Rainwater captures oxidized mercury, returns to water where it is taken up and biomethylated by marine organisms • Used in control instruments, tubes, rectifiers, thermometers, barometers, sphygmomanometers, germicidal and bactericidal agent • Dental amalgams, plating, jewelry, tanning, taxidermy, vaccines (thiomersal) • Industrial: fluorescent light bulbs, electric meters, batteries, antifouling agent in paints, slimicide in paper production, catalyst in plastic production • Agricultural: delay seed germination, inhibit fungal growth • Herbal medications • Workers involved in extraction of Hg • Maintenance work on furnaces and flues • Chloralkali workers • Alkyl mercury compounds in fungicides, paints, plastics
Kinetics	• Elemental form is inhaled (not ingested), alkyl mercury absorbed through all routes • In vivo inorganic to organic and vice versa conversions occur (mixed symptomatology)
Mechanism of action	• Inorganic and aryl mercury bind to –SH and interfere with enzymes • Metallothionein binds mercury and protects kidneys • Longer alkyl and aryl Hg compounds are converted to inorganic Hg • Organic Hg is taken up by RBCs and accumulates in brain • Mercury compounds are eliminated slowly in urine, feces, saliva, sweat (organic excreted in stools, only 10% in urine)
Clinical	• Erethism (inhalation of mercury vapor): gingivitis, tremor, neuropsychiatric illness • Acrodynia or pink disease (inorganic mercury): hypersensitivity reaction characterized by painful, red fingers and toes with desquamating skin rash • Elemental: lungs, CNS, (PN, renal) • Inorganic: pulmonary, renal, gi, neurologic (neuropsychiatric, cerebellar, PN), salivation, sweating, gingivitis, red brown lens pigmentation, blue teeth or gum pigmentation, corrosion • Organic: delayed progressive CNS damage - cerebellar features, constricted fields, central hearing loss, rigidity, spasticity, circumoral and acral paresthesias, explosive behavior, insomnia, skin, rarely kidneys, may be fatal • No measurable clinical effects of amalgams • No evidence of toxicity from thiomerosal in vaccines
Laboratory	• Hypoxia and pulmonary infiltrates

	• Proteinuria • Bloog and urine Hg levels
Prevention	• Ventilation and respiratory protection, control of industrial emission • Medical surveillance and biologic monitoring • Decontamination
Management	• DMSA, DMPS, BAL, penicillamine • Alkyl mercury does not respond to chelation • Dialysis with renal failure
Additional comments	• Only metal that is liquid at room temperature • Methyl mercury containing fungicides are no longer used in US

- ***Summary of the toxicity related to different forms of mercury***[21, 26]

	Elemental mercury	**Inorganic mercury**	**Organic Mercury**		
Source	Dental amalgam, thermometers	Mercury salts (e.g.: mercuric chloride)	Methyl mercury (seafood)	Ethyl mercury (preservative in Thimerosal in vaccines)	Dimethyl mercury
Most relevant route of exposure	Inhalation or dermal absorption of vaporized form, Limited ingestion of liquid form	Ingestion (also dermal contact and inhalation)	Ingestion	Ingestion or parenteral	Inhalation or transdermal
Toxicity	Lungs, CNS, PNS, renal, skin	Gastrointestinal, kidney, skin, CNS	CNS (cerebellum, calcarine cortex)	CNS (cerebellum, calcarine cortex), gastrointestinal, renal, skin	CNS (cerebellum, calcarine cortex)
Monitoring	Urine and blood mercury	Urine and blood mercury	Blood mercury		
Additional Comments	Liquid at room temperature; if ingested, it is poorly absorbed and excreted in the feces	Mercury salts can be corrosive	Toxicity may be delayed by weeks or months; primary route of excretion is fecal		

- ***Other metals with neurotoxic potential: Sources and neurologic toxicity of other metals*** [20, 21]

	Sources of toxicity (and potential uses)	**Clinical features**	**Additional comments**
Aluminum	Aluminum-containing dialysates Parenteral nutrition Consumption of food prepared in aluminum vessels Workers subject to industrial exposure	Dialysis encephalopathy or dialysis dementia *Pot room palsy* (workers in the pot room of aluminum smelting plants, characterized by memory difficulties and incoordination) Osteodystrophy and microcytic anemia	Serum aluminum concentrations do not accurately reflect total body burden Deferoxamine is the preferred chelator
Barium	Diagnostic radiology Industrial uses (ceramics, bricks, tiles, plastics)	Barium induced paralysis (mediated by hypokalemia), areflexic quadriparesis Respiratory failure due to muscle weakness Rhabdomyolysis	Potassium is an effective antidote

		GI hemorrhage, cardiac arrhythmias, renal failure	
Bismuth	Bismuth salts are used in the treatment of gastric ulcers, diarrhea, and *Helicobacter pylori* infection Fire detection systems, electrical fuses, and as an alloying agent.	Encephalopathy Gastrointestinal symptoms, renal insufficiency, increased salivation, and skin rash	CT: Hyperdensities in the basal ganglia, cerebellum, and cerebral cortex Possible role for some chelators (DMSA and DMPS)
Cadmium	Nickel-cadmium batteries Stabilizer for polyvinyl chloride Component of alloys Paint pigments	Disequilibrium and PN Acute respiratory failure, renal toxicity, painful bone disorders	Toxicity due to inhalation or ingestion Blood cadmium concentrations are indicative of recent exposure Urinary cadmium concentrations reflect total body burden
Lithium	Lithium hydride is used in batteries, alloys, glasses, and ceramics Lithium chloride and bromide are used in air conditioning Lithium carbonate is used as a mood stabilizer and in the prophylaxis of cluster headaches	Lithium neurotoxicity occurs in context of chronic therapeutic use or acute ingestion Acute toxicity: gastrointestinal symptoms Chronic toxicity: nausea, polyuria, somnolence, tremors, myoclonus, seizures, cardiac arrhythmias, nephrogenic diabetes insipidus, hypothyroidism	Toxicity due to ingestion or inhalation Neurotoxicity may be seen even at therapeutic concentrations, particularly in the elderly and in patients on neuroleptics No specific antidote is available Correction of dehydration and management of nephrogenic diabetes insipidus
Phosphorus	Fireworks and rodenticide pastes	White phosphorus: burns and injury to the lungs, kidneys, liver, and gastrointestinal tract Chronic exposure is associated with an occupational illness called *phossy jaw* Restlessness, irritability, drowsiness, stupor, and coma	Toxicity due to dermal absorption or ingestion Serum phosphorus concentrations may not be useful in making the diagnosis
Platinum	Platinum is used in jewelry, laboratory equipment, electrical contacts, and dental fillings Neurotoxicity due to platinum occurs from use of cisplatin, carboplatin, and oxaliplatin	Affect the dorsal root ganglia or large myelinated sensory axons Cold-induced paresthesias (oxaliplatin) Coasting Nephrotoxic, ototoxic, and emetogenic potential	Carboplatin is less toxic than cisplatin
Selenium	Selenium is used in the vulcanization of rubber, as a decolorizer of glass, in electronics, and in antidandruff shampoos	Acute toxic exposure: garlic odor, hair loss, nail discoloration, teeth decay, gastrointestinal, and pulmonary distress Chronic toxicity: due to high dietary selenium has been	Deficiency has been associated with a cardiomyopathy and endemic disease in China called *Keshan disease* (nausea, vomiting, and myocardial necrosis)

		associated with PN	
Silver	Silver is used in photographic films and electronic products Component in alloys, solders, sterling ware, and jewelry Antibacterial agent	Irreversible blue-grey pigmentation of skin (argyria), PN, seizures	Toxicity can result from dermal absorption, inhalation, or ingestion
Tellurium	Tellurium is used as a steel additive and is alloyed with aluminum, copper, lead, or tin Used in vulcanizing rubber, in the manufacture of thermoelectric devices, and as a coloring agent in glass and ceramics	Garlic-like odor (tellurium breath) Headache, drowsiness, and dizziness Anhidrosis, hair loss, dry mouth, and blue-black skin discoloration	No effective treatment
Thallium	Thallium is used in alloys, smelters, photoelectric cells, optical systems, semiconductor industry, cardiac imaging The use of thallium and its compounds as pesticides and as a depilatory agent has been banned	Thallium ingestion can cause acute gastrointestinal symptoms, renal failure, alveolar damage, hepatotoxicity, cardiovascular collapse Painful, distal, predominantly sensory PN CNS: psychosis, convulsions, ataxia, tremor, optic neuropathy, and autonomic dysfunction Alopecia	Toxicity can result from dermal absorption, inhalation, or ingestion Blood Thallium concentration reflects recent exposure Prussian blue (potassium ferric ferrocyanide) given soon after ingestion binds with thallium in the intestines and increases fecal excretion Potassium chloride will exchange with thallium in cells and increase renal excretion
Tin	Organotin compounds have been used in the plastic industry and as agricultural chemicals Trimethyl and triethyl tin compounds are found to be extremely neurotoxic	Trimethyl tin produces a limbic cerebellar syndrome with seizures and a mild sensory neuropathy Triethyl tin is myelinotoxic and produces edematous and vacuolar changes in central myelin Skin and eye irritation, a form of pneumoconiosis (stannosis), gastrointestinal effects, and proximal tubular damage	Toxicity can result from dermal absorption, inhalation, or ingestion The neurotoxicity of tin is due to the organotin compounds
Zinc	A commonly used supplement for a variety	Myeloneuropathy	Proximate mechanism is copper deficiency

	of conditions like common cold prevention

- ***Common neurologic symptoms and signs due to industrial and environmental toxins***

Adapted from[19, 21, 22, 27]

Syndrome	Localization	Clinical Presentation	Examples
Acute encephalopathy	Diffuse; cerebral hemispheres	Varying combination of headache, fatigue, irritability, disorientation, amnesia, ataxia, slurred speech, psychosis, anxiety, depression, convulsions, stupor, coma	Acute encephalopathy due to metal fumes exposure is rare
Chronic encephalopathy	Diffuse; cerebral hemispheres	Varying combination of cognitive and psychiatric disturbances or nonspecific symptoms including headache, fatigue, memory disturbance, insomnia, irritability, and changes in mood or personality	Lead, particularly in children
Parkinsonism	Basal ganglia	Tremor, rigidity, bradykinesia, postural instability	Manganese,
Myeloneuropathy	Spinal cord and peripheral nerves	Gait ataxia, hyperreflexia, Babinski sign, paresthesias, sensory loss, weakness	Zinc
Polyneuropathy	PNS and ANS	Paresthesias, numbness, weakness, decreased or absent reflexes, autonomic dysfunction	See next table

- ***Toxic neuropathies due to common industrial and environmental toxins***

Adapted from[21, 27]

Type of neuropathy	Examples
Predominantly motor or sensorimotor with significant weakness	Arsenic, lead, mercury
Predominantly sensory or sensorimotor with minimal weakness	Arsenic, lead, mercury, thallium
Sensory neuropathy or neuronopathy without weakness	Platinum based drugs
Cranial neuropathy	Thallium
Prominent autonomic dysfunction	Thallium

- ***Laboratory diagnosis of heavy metal toxicity***[21, 28]

Hair and nail determinations are generally of limited utility due to concerns regarding possible external contamination. Urinary metal excretion rates following provocative chelation (chelation challenge test) has significant interpretive difficulties and is of limited diagnostic utility. Spot urine measures are less reliable than 24-hour urine determinations. Expressing urinary excretion in terms of grams of creatinine excreted reduces variability introduced by dilution. Meticulous attention should be paid to specimen collection and metal free collection devices and storage tubes should be used. Unexpected results should prompt repeat testing due to the possibility of specimen contamination. Reference ranges vary considerably from laboratory to laboratory. The normal values shown here are those used at Mayo Medical Laboratories.

Metal and Normal values	Comments
Arsenic	
Blood: <0.07 μg/ml; Urine (μg/24 hours): <120 (inorganic: <25); Hair or nail (μg/g dry weight): <1	Blood As becomes "normal" within hours after exposure; ingestion of seafood results in elevated urine As due to the nontoxic organic form
Lead	
Blood: Children <10 μg/dl, Adults <20 μg/dl; Urine (μg/24 hours): <80; Hair or nail (μg/g dry weight): <5	Pb concentrations greater than 20 μg/dl in children and 70 μg/dl in adults are considered toxic; blood Pb concentrations indicate recent exposure or lead mobilization from bone stores; urinary Pb excretion over 400 μg/24 hours is abnormal (excretion of up to 125 μg/24 hours is probably not associated with significant poisoning)
Manganese	
Serum: 0.4-0.85 ng/ml; Urine (μg/24	Specimen contamination can easily occur; individuals with significant Mn

hours): <2 **Mercury**	exposure excrete over 10 µg/24 hours
Blood: <10 ng/ml; Urine (µg/24 hours): <20; Hair or nail (µg/g dry weight): <1	Blood Hg levels may be elevated for 2 to 3 days after a seafood meal; significant exposure is indicated when blood Hg is over 50 ng/ml for alkyl mercury and over 200 ng/ml for inorganic Hg; the lowest concentration at which toxicity maybe apparent is over 50 µg/l (generally seen with values over 300 µg/l); urinary mercury concentrations correlate well with exposure to elemental or inorganic Hg (urinary excretion accounts for less than 10% of methyl Hg excretion)

- ***Properties of commonly used chelating agents*** [21, 29]

When dealing with metal toxicity, chelation therapy represents a secondary form of treatment and is most effective when administered shortly after exposure. Metals exert their toxic effect by combing with a ligand essential for normal physiological functions. Chelating agents are metal antagonists that compete with ligands for the metal, form complexes with the metal, and increase excretion of the metal. This may not lead to improved neurological outcome. Chelation therapy can sometimes be associated with a transient worsening of symptoms, attributable to the initial mobilization of the toxic metal. Depletion of other metals like zinc or copper may be seen.

Chelating agent Route	**Use**	**Dose**	**Common side effects**	**Comments**
$CaNa_2EDTA$ diluted in 5% dextrose or 0.9% saline **IV, IM**	Pb	*Lead:* 30 to 50 mg/kg/day as continuous infusion or in 2 -3 divided doses IM X 5 days Maximum /d dose: 2 g	Nephrotoxicity, excessive thirst, chills, fever, myalgias, nausea, nasal congestion, hypotension, cardiac arrhythmia, mucocutaneous lesions (?Zn deficiency), headache, paresthesias	Stop infusion for 1 hour before blood Pb concentration to avoid falsely elevated reading Laboratory abnormalities with $CaNa_2EDTA$ therapy: anemia, leukopenia, glycosuria, ↑PT, ↑liver enzymes Not effective in Hg poisoning because Hg is sequestered in body compartments not penetrated by $CaNa_2EDTA$ and Hg is tightly bound to ligands like –SH Not metabolized (Alternative: 1000 to 1500 mg/m^2/24 hr iv or as a 30 minute infusion given daily for 5 days)
BAL 10% (100 mg/ml) solution in oily liquid **IM**	As, Pb, Hg	*Typical:* 2.5-5.0 mg/kg IM q 4 hrs X 2 days, then 2.5 mg/kg q 12 hrs on day 3, and 1 to 2 X a day thereafter for 1-2 wks	Hypertension, tachycardia, nausea, vomiting, abdominal pain, transient oral burning and salivation, sweating, skin reactions, fever, headache, convulsions	Contraindicated in peanut allergy Avoid in hepatic or renal injury Hemolytic anemia with G6PD deficiency The dimercaprol-metal chelate is more stable at a higher pH. Maintenance of alkaline urine may prevent liberation of the metal in the kidney. (Alternative: 75 mg/m^2/4 hrs iv with a total daily dose of 450 mg/ m^2)
DMSA 100 mg capsules **PO**	As, Pb, Hg	*Children:* 10 mg/kg tid X 5d, then bid X 14 d *Adult:* 100 to 200 mg po bid (maximum: 500 mg po bid)	↑aminotransferase, nausea-vomiting, diarrhea, ↓appetite, metallic taste, rash, paresthesias, lacrimation-rhinorrhea	May follow use of BAL or EDTA when initial parenteral therapy is required Sulfur like odor to body fluids may limit compliance Thrombocytosis, eosinophilia, neutropenia subside when therapy is discontinued Metabolized to mixed disulfides of cysteine which may be the active chelating moiety
DMPS	As,	*Acute:* 100 to	Elevated	Not approved for use by FDA, can be

PO, IV	Pb, Hg	250 mg IV over 5 mts every 3-4 hours, ↓ dosing after day 1 *Chronic:* 100- 200 mg tid-qid	aminotransferase, fever, rash, hypotension, burning of eyes and mouth	compounded for individual patients
Penicillamine 125 and 250 mg caps 250 mg tabs **PO**	As, Cu, Pb, Hg	1 to 2 g/day PO in divided doses	Hematologic, dermatologic, neurologic, renal toxicity and gastrointestinal side effects	Periodic monitoring of cell count, renal functions, and urinalysis Also chelates essential metals like cobalt and zinc

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