HOT TOPICS IN NEUROTOXICOLOGY
PB, CO and Mn

Jonathan S. Rutchik, MD, MPH
NEUROLOGY, ENVIRONMENTAL AND OCCUPATIONAL MEDICINE ASSOCIATES

20 Sunnyside Avenue, Suite A-321
Mill Valley, CA 94941, USA
TEL: 415-381-3133
FAX: 415-381-3131
jsrutch@neoma.com
www.neoma.com
OUTLINE

• CLINICAL CASES:
  – CASES IN LEAD TOXICITY: MOOD, TREMOR, NEUROPATHY
  – CASES IN CARBON MONOXIDE TOXICITY: ENCEPHALOPATHY, TREMOR
  – CASES IN MN TOXICITY: WELDERS AND STEEL CUTTERS: TREMOR, PARKINSONISM AND MOOD CHANGES
  – DISCUSSION AND QUESTIONS
LEAD EXPOSURE

• 44 RH Male flux maker using granulated lead, silica and borax, and soda ash presented with 4 months of headache, nausea, stomach problems for many months. No PMH.

• Lead blood level found to be 133 after 12 months of working

• Taken off work
PRESENTATION

- Mood changes
- Headache
- Bilateral UE tremor
- Numbness and tingling in feet
- Erectile dysfunction
Clinical course

- Chelated by medical provider with DMSA, succimer, Chemet for 19 days then on two more occasions
- PbB reduced to 54 ug/dl, then 43 and 35
- XRF performed and was elevated for bone lead
Examination

- Mild depression.
- 5-/5 weakness of the Interossei.
- SENSORY: RUE REDUCED pp, lt touch, T below the right elbow. Reduced T below bilateral knees. VIB below the right knee > L. PP right worse than the left below the knee.
- BRISK REFLEXES WITH NO CLONUS
- RUE tremors both at REST on the R > L as well and in ACTION and POSTURE.
- Mild dysmetria in the RUE, that is abnormal FNF.
- RESTING tremor was flexion extension type at wrist and medium amplitude; not pill rolling.
VIDEO
LEAD

- Ingestion, inhalation (inorganic) derm absorption (organic)
- Increased with Fe, Ca, Zn deficiency
- Heme synthesis, D-ALA, ferrochelatase
- Inhibits Na/K pump
- Cholic, diarrhea, constipation, headaches, vertigo, ataxia, seizures
- Renal effects, infertility, etc
Assessment

• Acute exposure: BLOOD
  – Childhood, >10 ug/ml concerning
  – Adults > 20 headache and performance> 60, cholic, anemia, renal >80 hospitalization with chelation

• Chronic exposure: Zinc Erythrocyte protoporphyrin

• Retained cumulative dose: Tibial lead (x-ray florescence)
XRay flourescence of long bones

- The concentration of lead in bone is associated with a decrease in hematocrit and hemoglobin levels in patients with low blood lead levels.
- Peak tibial lead, an extrapolated value from current values using year from last exposure, was consistently associated with impaired performance in the modalities of manual dexterity, executive ability, verbal intelligence and verbal memory.
EMG results

- Normal motor studies
- Reduced amplitudes and some sensory slowing of the lower extremity studies
- Upper extremity ulnar sensory and median sensory asymmetrically suggestive of entrapment neuropathy
- Overall evidence of sensory demyelination and mild axonal changes
Patient is a 45 year old RH male flux manufacturer who complains of constant headache. Reduced sensation in both feet. Symptoms since before August 2005. Patient status post right knee arthroscopy March 1998. Patient PMH negative for Diabetes and/or thyroid disorder. Exam revealed full power, reduced temperature, light touch and pin prick as well as vibration and JPS in the LEs, with mild increased reflexes in the LE bilaterally. Ataxia is noted with tremor R>L which is unchanged with posture as well as some reduced RAM and RSM on the RUE with no increased tone.

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**SMALL SENSORY AMPLITUDES**

UC Davis OEM
May 2009

JS Rutchik, MD, MPH
Neoma.com
TREMOR and LEAD

• Sensory neuropathy
• Medications
• Mn, CO, MeCl2, Hg
• Association between BPb concentration and Essential Tremor. Increased exposure to lead or a difference in lead kinetics in ET?
Lead and Neuropathy
Parry 2007

• Motor neuropathy: short-term exposure to high lead concentrations; prognosis is good with termination of exposure
• Distal sensory and motor neuropathy: after many years of exposure, evolves more slowly, recovers less certainly.
• Lead intoxication in humans causes axonal degeneration but in other species, primary demyelination.
• Rubens 2001: mild sensory and autonomic neuropathy features more common than motor neuropathy classically attributed to lead
REFERENCES


REFERENCES ii


Carbon Monoxide Toxicity

- Cases
- Presentation and Acute Treatment
- Calculating and or estimating exposure
- Hyperbaric Oxygen: Role in acute and nonacute cases
- Neuropsychological testing
- Movement disorders and CO
- Prognosis
CO exposure

• 40 yr old M delivery person; found unconscious. HbCO 39%
• 45 yr old F lab scientist with dizziness, confusion and headaches.
• 60 yr old F with chronic flu like symptoms, headaches and depression
• 25 and 40 yr old Fs out all night awake found stuporous in a hotel with a broken heater. HbCO 13.7 and 10.
• 53 yr old M with RUE tremor and acute delirium. HbCO 19
CONCRETE CUTTER

• 53 MALE with no PMH develops new onset right arm shaking after nearly fainting while spending 30 minutes in an enclosed space cutting concrete with a gas powered saw.
• Colleague leaves work setting after 15 minutes.
• O2 given. In ER HB CO noted to be 19, 2 hours later.
VIDEO PATIENT ONE
Clinical presentation

*Increasing intensity of exposure*

1. Headache, fatigue, lightheadedness
2. Flushing, flu like symptoms, tachycardia, lowered bp
   1. (rare: cherry red skin, membranes, retinal hemorrhages)
3. Throbbing headache
4. Reduced vigilance, manual dexterity
5. Nausea, vomiting, coordination, fainting, coma, convulsions, pulmonary edema, death
Clinical

- HBCO: Signs/ severity not always correlated
- HBCO 4-5%: Decreased aerobic work capacity.
- > One hour of exposure = increased morbidity
- CAD history: Sx more dramatic
- Fatal cardiac arrhythmias and death at levels >50,000 ppm before elevated HBCO detectable.
LABORATORY/ URGENT ISSUES

• Blood gas: Decreased O2 saturation and metabolic acidosis; anion gap \((\text{Na} - \text{Cl} - \text{HCO}_3^-)\)
• Blood COHb assessment ASAP.
• Smoker?
• HALF LIFE: 7 hours normal
  – 2 hours with 100% O2
  – 30-50 minutes with hyperbaric
Mixtures

- **Smoking**
- Asphyxiants can further displace O2 leading to more hypoxia
- Enhanced by other exposures, NiCO4 (nickel carbonyl)
- Results from exposure, MeCl2 (paint remover). Product of hepatic metabolism. CO limits should be adjusted downward.
HYPERBARIC OXYGEN

• If exposure was <6 hours prior; HBO can reduce delayed neuropsychological chronic effects

• Use supported in:
  – Pregnancy
  – Change of mental status
  – Neuropsychological abnormalities, specific test battery
  – CO HB > 20 (ischemic ht dz or 40)
  – Unresponsive to 100% O2 acutely

• Reduces half life of CO by >50%. 
Hyperbaric O2

• Can help symptoms but unclear influence on delayed sequella or mortality in non life threatening cases.
• No clear benefit for those who did not lose consciousness, none for brief small for coma, but did not compared regular O2 with hyperbaric (Raphael)
• Side effects include seizures, tension pneumothorax, tympanic ruptures, ear and sinus pain.
CALCULATING %COHB
Haldane

• %COHb = [CO]air (PPM) x KT (HRS)
• K = 0.048 FOR LIGHT WORK, 0.018 REST
• FOR 53 YR OLD: 19 = X(0.048)(0.5)
  • X = 791 PPM!!!
• FOR 40 YR OLD: 39 = X(0.048)(0.1)
  • Y = 8125 PPM!
NEUROIMAGING
SEE WEAVER 2009

• CT: Infarction
• MRI: normal, diffuse atrophy, bilateral GP/basal ganglia changes; inc T2 signal (H2S and methanol). More likely to have poorer outcomes. Hippocampal atrophy on T2.
• MRS: (n- acetyl aspartase, a nonspecific neuronal marker) normal or decreased in basal ganglia
• EEG: Diffuse slowing acutely.
Neuropsychological testing: CONSB

- general orientation
- digit span
- trail making*
- digit symbol
- aphasia and
- block design
- mini mental.
- *Improved post HBT on trails.
Impairments

• Neurobehavioral, Visual, auditory discrimination
• 10-30% develop delayed Npsychological syndrome over 3-240 days.
• Peripheral neuropathy: *(Choi 1982, 0.84% with NCV and EMG changes)*
CO

Preexisting issues, medical conditions?

• Prognosis; age, prior medical and psychological history
• Parkinsonism reported, L dopa unresponsive
• Assess consistency with condition and exposure
• Post traumatic stress and somatiform issues +/- litigation
Carbon Monoxide

- Odorless, colorless and non irritating
- Product of combustion
- Binds to Hemoglobin; interferes with O2 carrying capacity
- Numerous deaths each year; 56,000 1979-1988
- Improper ventilation in workplace
- Faulty gas heating units or indoor wood or coke burning stoves
Carbon Monoxide

- Toxic at low levels: 0.1% in air leads to COHb of 50%.
- Odor threshold 10,000 ppm.
- OSHA PEL 8 hour of 50 ppm
- NIOSH REL 10 hour of 35 ppm, 15 minute ceiling of 200 ppm, IDLH 1200
MOVEMENT DISORDERS and CO

• Movement disorders ARE RARE, but have been described.
• Most onset of 2-8 weeks post exposure.
• Neuroanatomical localization to the basal ganglia. MRI, MRS.
  – The prevalence of tremor 33 years after CO exposure was noted in 10% of a large group in Japan. (Mimura et al 1999). Park and Choi in 2004 reported 6 patients with chorea with a latency 10-30 days.
• Usually good prognosis
• Tremor has not been reported immediately following an acute exposure.
VIDEO TREMOR II AND III
References CO

• Weaver L. CO Poisoning. NEJM. 2009; 360: 1217-1230
Clinical history of patient
*Rutchik JS ICOH Milan, Italy 2006

• 55 RH steel cutter, ^ PbB, leg tremors.
• Exam: Decreased RAM L arm. 6 months, rigidity, pain and dystonic posturing. Tremor assymetric, L arm, leg.
• Difficulty with memory, no PI
• MnB normal; Pb <20 ug/dl. Brain MRI WNL
• Removal from work, DA agonists, levodopa, anticholinergics to no improvement.
Occupational history

• Company confirmed materials included Mn
• PPE in the 1990’s.
• Reported frequent dizziness, night sweats.  
  10 year history of ^ PbB > 40 at work.
• No PMH, FH of neurologic/ psychiatric dz.
• The patient remains disabled.
STEEL CUTTER VIDEO
Note RT, dystonia, good balance
Parkinson’s Disease (PD)

- **1817 Shaking palsy: J Parkinson**
- 2 of 3: Bradykinesia, Tremor, Cogwheel rigidity. Also postural instability notable.
- Progression
- Positive response to L-dopa
- Defined by asymmetry, **but only in 70%**.
- Early resting tremor; not head titubations.
- Idiopathic: Unknown etiology, not the clinical exam, pathology or findings. (IPD)
PD- CONTINUED

• True PD: on off phenomena, hallucinations, dystonia reported in patients on medication.
• Prevalence: 7th decade (50/100,000)
  – 3-4/100,000 < 40
• Symptomatic medication benefit 6-12 mo.
• Pathology: Lewy inclusion bodies pathognomonic in pars compacta of the substantia nigra, and locus ceruleus
UNIFIED PARKINSON’S DISEASE RATING SCALE (UPDRS)

• UTILIZED FOR PATIENT CARE AND DRUG TRIALS (PROGRESSION, CHANGE)
• ASSESSES MOTOR ASPECTS OF PARKINSONISM
  – RIGIDITY
  – TREMOR
  – POSTURAL INSTABILITY
  – BRADYKINESIA
• NOT SPECIFIC FOR IDIOPATHIC, ATYPICAL PD
Parkinsonism

Parkinson’s Disease

Idiopathic PD

Genetic Forms

Genetic Forms%

Atypical P-ism

% PINK1 Form

*Parkin Form
UK Brain Bank Criteria for PD

Clinical Definition  Hughes 1992

- Bradykinesia
- One of three:
  - Muscular rigidity
  - Tremor, 4-6 Hz
  - Postural Instability
- Three of More Required
- Unilateral onset
- Rest Tremor
- Progressive
- Persistent Asymmetry
- Excellent Resp to L DA, for 5 years
- LDA induced severe chorea
- >= 10 year clin course
Exclusion criteria: UK BB PD

- Hx of:
  - Repeated strokes and stepwise progression
  - Repeated head injury
  - Definite encephalitis
- Oculogyric crisis
- Phenothiazine medication at onset of sx
- > 1 affected relative
- Sustained remission
- Strictly unilateral at 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Severe autonomic involvement
- Early severe dementia
- Babinski’s sign
- Presence of cerebral tumor or hydrocephalus
- Negative LDA response to large dose
- MPTP exposure

OHSC 2009
Atypical Parkinsonism

• Multiple System Atrophy (MSA):
  – Rapid progression. Poor response to L Dopa.

• Progressive Supranuclear Palsy (PSP):
  – Encephalopathy, posture, speech and swallowing. Rapid progression. Poor response to L dopa.

• Vascular Parkinsonism:
  – LEs, lack of rest tremor; strokes by history.

• Corticobasal Ganglionic Degeneration:
  – Older onset, rapid progression to death. Severe rigidity, dystonia, myoclonus, sensory findings and apraxias.

• Dementia with Lewy bodies:
  – PD with dementia within 12 months; hallucinations and fluctuating alertness.
Other causes of PD/ Pism

- Strokes
- Infections
- Tumor
- Alzheimer’s Dementia
- Boxing/ Head trauma
- Antipsychotic medications

- MPTP
- Carbon Monoxide
- Rotenone (Pesticide)
- Methylene Chloride
- Solvents
- Ephedrone
- Manganese
- Dx of Exclusion (IPD)
Clinical and Pathological criteria:

Not a hard and fast rule: Hughes 1992 and 2001:

- **1992**: 100 patients with PD; 76 autopsy (+)
- Reviewed charts: 89/100 had clinical PD
  - 73/89 had autopsy (+).
  - *67% of misdiagnosed had marked improvement from an initial response to Levodopa*.
- **2001**: 90/100 had autopsy (+). 10 misdiagnosed; 1 stroke.
- Movement specialists, 98.6 PPV
There is no PD: Weiner et al 2008

- No universally accepted neuropathological criteria for PD. All the accuracy studies reported are flawed. (Litvan 2003; Movement Dis, Task Force on Clinical Diagnostic Criteria for PD)

- Definition in question since different genetic LDA responsive PD (similar to IPD) or atypical forms
  - (A- synuclein, Parkin, PINK1, LRRK2, DJ1)

- Some forms do not contain Lewy bodies
MRI/ PET and PD

- PD postulated to be SN outflow problem (typical) versus BG receiving, processing problem (atypical)
- Presynaptic syndrome (L DA responsive)
- MRI +/- abnormal in SN
- PET reveals presynaptic syndrome (typical PD) versus post synaptic syndrome (atypical syndrome)
Manganism in Miners, Grinders, Welders

- **1837**: PD syndrome in Mn crushers.
  - Couper

- **1950s**: Miners;

- **1970s**: Ferroyalloy plants and battery plants.

- **1990s**: Welders.
Manganism
Canavan et al, 1934

- 55 Male, clumsiness and stiffness.
- Separation of ores for 3.5 years
- Exam: lack of expression, no tremor, foot slapping gait and marked propulsion to walk on his toes.
- No improvement over 13 years, died.
- Pathology noted frontal atrophy with reduced size of basal ganglia.
Manganism is *Atypical PD*

Manganese. In Feldman RG. “Occ and Env Neurotoxicology.” 1994

- Behavioral presentation. Compulsive laughter and hallucinations.
- Motor disturbances. Tremor, dysarthria, gait disturbance, slowness and clumsiness and postural instability.
- Psychosis subsides and dystonia may appear accompanied by awkward high stepping dystonic gait, different than IPD patients.
- Progression slower than IPD.
- *Mn possibly accelerates onset of IPD*
EXAMINATION

• PD
  • Resting tremor
  • Asymmetry
  • Cogwheel Rigidity
  • Bradykinesia
  • Age of onset \( \geq 60 \)
  • Progression

• Manganism
  • AT/ PT > RT
  • Symmetrical findings
  • Rigidity
  • Bradykinesia
  • Age of onset <50
  • Progression minor
Clinical features: MIMD and PD
Similar or different

• Emara 1971: Dry battery worker hemiPD.
• Smyth 1973: 5 cases in ferromanganese alloy workers, some with unilateral presentations and lacking in depression, sleep issues or autonomic dysfunction. “Indistinguishable from PD”
• Wang 1989: Parkinsonism was noted in 6 of 8 welders “well under the usual age of onset of idiopathic Parkinson’s Disease.”
Similarities and differences

• Huang 1989: Patients responded to LDA, with normal cognitive functions. “clinical picture of resembled PD.”

• Huang et al in 1993: “Chronic manganism may overlap with Parkinson’s Disease, progressive and response to levo dopa was initially positive but that they did not develop dyskinesia.

• Huang 2007: 2/4 with hemiPD
MANGANISM: VARYING PRESENTIONS


• 6 Patients (4 welders) EVALUATED IN GUANXI PROVINCE, CHINA WITH MN EXPOSURES

• 3 HAD EVIDENCE OF CLINICAL PARKINSONISM BY UPDRS, 2/3 WITH ELEVATED MNB, 1/3 WITH MRI WITH BILAT GP ABNORMALITIES
MANGANISM: VARYING PRESENTIONS

*Rutchik et al; Pending publication

- **UPDRS POSITIVE:**
  - 1/3 PRESYNAPTIC, (PD)
  - 2/3 POST SYNAPTIC (ATYPICAL PD)

- **UPDRS NEGATIVE**
  - 3/6 WITH TREMOR

- **AVERAGE AGE WAS 56**
VIDEO:
GUANXI ATYPICAL PD;
ore crusher: B RT, PT, abnl
MRI GP, elevated Mn B
Axial T1-weighted images (left) and a normal volunteer (right). Symmetric high T1 signal intensity within the globi pallidi compared to surrounding white matter.
VIDEO
Guanxi welder with PD: masked facies, RT, 20 yr exposure, response to L DA
Pathology
from Barbeau, Adv Neurol 1976, Neurotox1984

• Manganese (Post synaptic)

• Basal Ganglia
• Pars reticulata, Substantia nigra
• Thalamus

• CONTRADICTION:
  – Lewy bodies found in ZC of SN! Bernheimer, JNS 1973

• PD (Presynaptic)
• Zona Compacta, Substantia Nigra
• Reduced dopamine in caudate and putamen
• Lewy bodies
Neuroimaging
from Calne D et al Neurology 1994
PRESYNAPTIC VERSUS POST SYNAPTIC

• PD
• MRI possibly abnormal in SN

• Manganism
• MRI abn for GP, striatum, SN, pituitary T1, normal T2. (Correlated with blood Mn levels, even normal workers)
• NORMALIZES IN 6 MONTHS
• SPECT normal
PET:
F- dopa: nigrostriatal pathway
Raclopride D2 receptors: post synaptic binding

- PD (Presynaptic)
- Fluorodopa PET **reduced uptake in striatum** (post putamen)
- Raclopride dopamine receptor marker **increased** in early untreated PD (up regulation of DA receptors) **reduced** in advanced disease

- Manganism (Post synaptic)
- Fluorodopa PET **normal**
- Raclopride binding **reduced**
PET and MIMD

- PET scans consistent with classical PD in welders
  - Wolters et al 1989
  - Kim et al 1999
Welders and MIMD


Welder and MIMD

• Racette, 2001:

• Case control, n=15. Welders with PD v IPD.

• Younger age of onset for Mn PD v IPD. Exams same. + L- Dopa response. PET 6 f-dopa: loss post putamn, c/w PD.

• Criticism: Could be coincidental exposure
Welder and MIMD

• **Koller, 2004:**

• 13 patients with Mn induced PD from welding exposure randomized to L- DA or placebo. Average age 61.2; welding years: 25.2.
  – 69% kinetic tremor, 58% symmetrical sx.
  – No differences for 3 doses; all no effects.
Welder and MIMD

- **Racette, 2005**: *Special criteria for PD not Pism*
- 1423 welders referred by attorneys, utilized UPDRS3 and video.
  - Took those with PD/ No. of welders in state to determine prevalence of PD in welders
  - Higher than general population (1985 study)
  - No correlation of welding hours, with UPDRS score, or diagnosis. Welding either increased prevalence at all ages, shift to younger age
Welders/ Manganese and PD

- Gorell et al 1997 and 1999 (> 20 yrs Mn)
- Lucchini et al 2003 (Env exposure to Mn)
- Smargiassi et al 1998 (metals)*
- Seidler et al 1996 (Mn)*
- Wechsler 1991 (Welders)*
- Zayed et al 1990 (AL, Fe and Mn)
- Park et al 2005 (Welders and MOR)
- Kirkey et al 2001 (Structural/ Welders)
- *Some had statistical challenges like no controls
No association Mn and PD

- Fored et al 2005
- Frigerio et al 2005
- Marsh et al 2006
- Goldman et al 2005
- Fryzek et al 2005
- Elbaz 2008

- Small amount of cases or no cases with controls, others suffered from a lack of sensitivity because of study design or other factors.
Neurologic evaluation of welders
Rutchik, JS*

- 293 welders (Western US) referred by plaintiff attorneys for neurologic evaluation
- 41 of 293 had UPDRS consistent with Parkinsonism
- Mean age of onset of symptoms was 47 (22-64)
- Mean duration of welding years was 22.9.
- 15 of the 41 welders reported > 50 % stick welding.
- 5 of the 41 reported only second hand inhalation at the work place.
Neurologic evaluation of welders
Rutchik, JS*

• 23/ 41 had confounders.
• 9: > 6 year latency of onset of symptoms after exposure ended.
• 6: had a FH of neurodegenerative disease.
• 2: onset of symptoms after the age of 60.
• 1 had severely progressive disease
• 3 had dementia along with parkinsonism
• 2 had insufficient welding or second hand welding exposure for consideration.
Neurologic evaluation of welders
Rutchik, JS*

- 18 with no confounders
- Mean onset of symptoms was 47
- Mean years of welding for this group was 22.9.
- Plan to compare to Racette 2005. Denominator to be all welders in CA (29800) and WA (pending #).
MANGANISM may present as…

• ATYPICAL PARKINSONISM (PD)

• SIMILAR PRESENTATION TO PARKINSON’s DISEASE (PD) WITH EARLIER ONSET OF SXS

• TREMOR, NEUROPSYCHOLOGICAL SYNDROME, WITHOUT CRITERIA FOR PD (UPDRS)
MANGANESE AND WELDERS
Dose and duration

- Types of welding processes: stick welding, TIG/ MIG, submerged arc.
- Hours each day and number of years
- Welders asst, mechanic, solderer; hrs near fumes
- Confined space hours
- PPE; SCBA, ventilation etc
- Metal fume fever symptoms
- Employment records: days out of work
- Latency to onset of symptoms
Manganism
Exclusionary factors

• ONSET OF SYMPTOMS: post exposure
• MEDICAL HISTORY:
  – Head trauma, diabetes, thyroidism
• MEDICATIONS:
  – Phenothiazines; Li, bp, albuterol, valproate
• OCCUPATIONAL HX:
  – Pesticides, CO, CS2, MeCl2
• FAMILY HISTORY of PD, ET or AD, etc
MANGANESE

• OSHA CEILING (5 mg/m3)
• ACGIH TLV (0.2 mg/m3)
• BEI: Blood v urine. Both have been used to assess workers. Mainly compared to subclinical test result to consider dose response result.
• Personal versus air sampling.
  – 62% of welders, Mn levels >0.2 mg/m3. *Susi 2000.
• Total breathable dust issue. IH issue!
Mn toxicology

• Blood Mn assess recent exposure
• Urine not best (bile to feces excretion)
  – ? appropriate for baseline and then Ca EDTA challenge (2X in chinese Mn patients)
• Fe metabolism alteration (also in IPD)
  – reduced transferrin receptor, but ^ ferritin and transferrin and increase Fe across CSF
• Fe mediated oxidative stress/ cell death
Mn toxicity and treatment

- L Dopa
- Ca EDTA may reduced Mn B; ? Sx
- Para aminosalicylic acid- TB medication
  - Ideal for chelation for metals
  - (chinese case of reduced symptoms- EPS and stable prognosis)
  - Mechanism: inflammatory process or chelation?
TREMOR VIDEOS
Guanxi patient with tremor only
MANGANISM AND TREMOR

– Patients with action or postural tremor, neuropsychological symptoms and exposure histories.
  - 100% of patients with asymmetric AT or PT develop PD after 10 years. *Chaudury, 2005

– Differentiate from ET and other tremors
– Assess blood and MRI
– Removal from exposure
– Re evaluation for PD findings.
Essential tremor

- Bilateral Postural or kinetic tremor of hands
- Isolated head tremor without dystonia
- Excluded by other neurological signs
  - Recent neurological trauma
  - Drugs, anxiety, depression, hyperthyroidism
  - Sudden onset or stepwise progression
  - Orthostatic tremor (lower extremities)
  - Position or task specific
  - Isolated voice, tongue, chin or legs
- Alcohol suppression not sufficient to include or exclude
Other types of tremor

• Medication induced.
• Neuropathic (diabetic tremor?)
• Physiologic, high frequency, hypoglycemia
• Psychogenic
ASSESSMENT OF WORKERS FOR MANGANISM

- Use of UPDRS to assess tremor, rigidity, gait and postural instability
- Consider removal from work, blood Mn, and neuroimaging (MRI and PET)
- Gather medical records
- Consider medicating with L Dopa.
- RE assessment
Steel worker case

- Presentation is atypical
- Younger than 60
- Symptoms developing during the course of his employment
- MRI and blood normal due to past exposure
- No response to medication.
- No confounding medical history.
- Confirmed Mn exposure, and lead exposure supports insufficient PPE.
- Plan: removal from occupation. Watchful waiting.
TOPICS FOR DISCUSSION

- What is a significant exposure history?
- What does it mean when a patient has normal Mn B and normal MRI?
- Could this be Mn induced?
- What about a PET c/w presynaptic PD?
- At what age of a presentation does one consider PD, Mn associated?
TOPICS FOR DISCUSSION

• What are normals for blood?
• What is a safe exposure level to Mn?
• What is a biomarker for Manganism?
• TREATMENT IMPLICATIONS?
Manganese references

• Michael Aschner, Tomás R. Guilarte, Jay S. Schneider and Wei Zheng. Manganese: Recent advances in understanding its transport and neurotoxicity. *Toxicology and Applied Pharmacology, Volume 221, Issue 2, 1 June 2007, Pages 131-147*


• Many more on request