Toxins - Diagnosis

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Overview

1. Acute Exposure Versus Body Load
2. Clinical Presentations
3. Conventional Lab Tests
4. Unconventional Lab Tests
5. Monitoring
Acute Exposure versus Body Load

• Must differentiate between acute exposure and body load
• Testing reveals exposure, not necessarily toxicity
  • In general, serum and urine levels represent acute exposure
  • Essentially no gold standard for body load
  • Serum, whole blood, hair, urine, feces, nails, and adipose have all been used for assessment
  • Challenge testing can reveal body load of metals

DeVito MJ, Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals. Environ Health Perspect. 1995
Rooney JP. The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. Toxicology. 2007
Early Clinical Presentations

- Immunological
  - Allergies, asthma, chemical sensitivity, chronic infections, autoimmunity
- Neurological
  - Headache, brain fog, balance, memory, mood lability, parkinsonism
- Endocrine
  - Hypothyroid, infertility, temperature dysregulation
Sample Questions for Toxic Metal Exposure

1. Has the patient knowingly been exposed to metals?
2. What is patient’s occupation (dentist, welder, ship builder, etc.)?
3. How frequently does the patient eat tuna, swordfish or shark?
4. Does the patient have mercury amalgam fillings?
5. If the patient is taking any dietary supplements, do they have certificates of analysis that they are free of contaminants?
6. Is the patient taking any Ayurvedic or traditional Chinese medicine dietary supplements?
7. Does the patient experience a metallic taste in their mouth and have not recently been taking medications documented to cause metallic taste?
8. Does the patient have a history of smoking (particularly high in cadmium)?

Neustadt J, Pieczenik S. Mercury—an example of heavy metal toxicity. IMCJ 2007;6:1
Clinical - Arsenic

- The most common neurologic effect of chronic arsenic intoxication is a sensory-predominant peripheral neuropathy in a “stocking-glove” pattern.
- Mechanism similar to neuropathy of thiamine deficiency: arsenic inhibits conversion of pyruvate to acetyl coenzyme A thus blocking Krebs cycle.
- Skin lesions:
  - Hyperkeratosis,
  - Hyperpigmentation,
  - Skin cancer

Cadmium Exposure Symptoms

Acute Exposure
- Virtually all industrial
  - Battery manufacture
  - Pigment manufacture
- Route important with air being common and especially toxic
- "the cadmium blues:” chills, fever, and muscle ache
- More severe exposures can cause tracheo-bronchitis, pneumonitis, and pulmonary edema

Chronic Exposure
- Few symptoms until significant kidney damage
- Osteoporosis and osteomyelitis
- Joint pain
- Hypertension
- Albuminuria
- Gout
Lead Toxicity Symptoms

- Blood levels limited to acute toxicity
- Symptoms correlate with degree of elevation

<table>
<thead>
<tr>
<th>Level of Toxicity</th>
<th>Blood Lead Concentration (µg/dL)</th>
<th>Clinical Presentation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or impaired abilities</td>
<td>&lt;10</td>
<td>Decreased learning and memory, decreased verbal ability, impaired fine motor coordination, signs of ADHD or hyperactivity, lower IQ, impaired speech and hearing</td>
<td>...&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mild</td>
<td>10–39</td>
<td>Myalgia or paraesthesia, irritability, mild fatigue/lethargy, occasional abdominal discomfort</td>
<td>...</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;40–50</td>
<td>Arthralgia, difficulty concentrating, general fatigue, headache, muscular exhaustibility, tremor, weight loss, vomiting, constipation, diffuse abdominal pain</td>
<td>Fatigue, somnolence, moodiness, lessened leisure interest, impaired psychometrics, chronic hypertensive effects, reproductive effects</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;70–80</td>
<td>Lead lines (blueish black appearance on gingival tissue), colic (intermittent, severe cramps), paraesthesia or paralysis, encephalopathy</td>
<td>Headache, memory loss, decreased libido, insomnia, metallic taste, abdominal pain, constipation, myalgia/arthritis, nephropathy</td>
</tr>
<tr>
<td>Severe, acute</td>
<td>&gt;100–150</td>
<td>Encephalopathy, seizures, anemia, nephropathy</td>
<td>Encephalopathy, various CNS effects, anemia, nephropathy</td>
</tr>
</tbody>
</table>

Gracia RC, Snodgrass WR. Lead toxicity and chelation therapy. Am J Health Syst Pharm. 2007 Jan 1;64(1):45-53
Mercury Neurological Symptoms

Online Neurocognitive Testing

CNS Vital Signs

- Finger-tapping test
  - Psychomotor speed
- Symbol digit substitution test
  - Processing speed
  - Several cognitive functions
- Verbal memory test
  - Recognize, remember and retrieve words
- Continuous performance test
  - Sustained attention, vigilance, and choice reaction time

Conventional Laboratory Tests

- Blood and urine levels of toxic metals
- Surprising number show toxin exposure
  - CBC: RBC, WBC, platelet count, hemoglobin, basophilic stippling
  - Liver enzymes: ALT, GGTP
  - Inflammatory markers: CRP
  - Lipids: LDL, oxLDL, triglycerides
  - Blood sugar: insulin, FBS, 2-hour PP
  - Metabolites: bilirubin, uric acid, 8-OHdG
- Within the “normal” range reflect toxin load
- The historic “normal” range has been changing as the population has become more toxic
Poor Hg Inter-Test Correlation

- Poor correlation between blood and urine, $r = 0.30$
- Better correlation between blood and hair, $r = 0.56$

## Basophilic Stippling of Red Cells

<table>
<thead>
<tr>
<th><strong>Toxins</strong></th>
<th><strong>Diseases</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>Alpha-thalassemia, HbH Disease</td>
</tr>
<tr>
<td>Lead</td>
<td>Beta thalassemia</td>
</tr>
<tr>
<td></td>
<td>Hereditary pyrimidine 5'-nucleotidase deficiency</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td></td>
<td>Sideroblastic anemia</td>
</tr>
<tr>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
</tbody>
</table>
**GGT: Indirect Measure of POPs**

- Glutathione is key intracellular defense against oxidative stress
- Cellular GGT metabolizes extracellular GSH, allowing precursor amino acids to be reutilized for intracellular GSH.
- **Exposure to POPs induces GGT as a defensive mechanism.**
- Within normal range predicts type 2 diabetes, coronary heart disease, hypertension, stroke, dyslipidemia, chronic kidney disease and cancer.
- **Men with GGT >50 U/l had ~26 fold risk for diabetes compared to those with <10. Those with 40-49 had a ~20 fold risk.**
- Levels within normal range occur with obesity, xalcohol, cigarette smoking, physical inactivity, high meat/low fruit and vegetable intake
- Cumulative biomarker for environmental pollutants.

GGT and Alcohol Consumption

- GGT directly correlates with alcohol consumption
- In a non-uniform population, 40 g/d will elevate GGT ~15%
- Watch for false negatives
  - Genomic variation
  - Are these the ones most sensitive to/damaged by chemical toxins?
- Could up-regulation of GGT in light alcohol consumption be reason for benefit?

GGT Levels Correlate with Risk of Death

- GGT over 50 associated with tripling of death rate!
- 30-40 associated with doubling

GGT Data from Canadian Oil Field Workers

GGTP

20-fold increased risk of diabetes
GGT From Small US Company with Young Workers
POPs and CRP Interact to Increase Insulin Resistance

Uric Acid: Indirect Measure of POPs

- Poly-fluorinated hydrocarbons (PFOA and PFOS) associated with increased serum uric acid


Steenland K et al. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. Environ Health Perspect. 2010 Feb;118:229-33.
ALT: Indirect Measure of POPs

- ALT (proxy marker) elevation in 10.4% (not including viral hepatitis, hemochromatosis, or alcoholic liver disease) of NHANES 03-04 subset
- Risk of elevated ALT increased dose-dependently with cadmium, lead, mercury, and PCB exposure
- 100% of individuals had detectable PCBs, 92.5% mercury, and 99.6% had detectable lead
- In 2005-08, prevalence of NAFLD in US was 11%, a growing cause of chronic liver disease.

Bilirubin as a marker of POPs

• Degree of serum bilirubin increase is prognostically significant in chronic liver dysfunction
• Mono-ortho PCB TEQ values were found to be significantly positively associated with bilirubin ($\beta=0.71$, $P=0.008$) following adjustment for multiple potential confounders.
• Bilirubin levels significantly correlated with PCBs -105,-118,-126, and -194
• Smoking appears to be the biggest confounder

Liver Enzymes Reflect Toxic Load

- AST, ALT and GGT increase with body load of PCBs and OCPs
- Some non-linear
- Oxychlordane top quartile:
  - ALT ↑10%
  - GGT ↑25%

LDL-Cholesterol as Measure of POPs?

- 5-year study to determine if POP levels predict future elevation in LDL-cholesterol
- 598 subjects initially at age 70
- Looked at 23 POPs
- Best correlation with PCB 194

oxLDL as Measure of POPs?

- 992 70-year old individuals (50% women)
- Sum of PCBs showed strong, significant positive associations with ox-LDL, and significant negative associations with glutathione-related markers (GSSG and GSSG/GSH)
- A number of POPs (PCB-99, 138, 153, 156, 170, 180, 194, 206 and 209) showed strong significant positive association with ox-LDL

WBC and PCB and OCP Exposure

- Strong inverse correlation with PCBs and OCPs and CBC
- Linear with almost all PCBs
- High variability with OCPs
- Within “normal” range!

Solvents Decrease Platelet Count

- Compared workers exposed 2.3 hr/day to those exposed most of day to toluene
- All wore face masks and protective gear
- Platelet count 14% lower: 252 versus 216/ml
- Impairment of sympathetic nerves (OR = 4.13)
- Impairment of peripheral nerves (OR = 6.94)
- Positive relationship between neurological abnormalities and a self-reported neuropsychiatric measurement (r = 0.35-0.66)

1. < 50, there is no difference between those with the lowest and highest PCBs
2. In youngest group, insulin production increases in response to toxin level
   - As expected since blocking of insulin receptor sites by PCBs requires more insulin
3. That adaptive ability decreases with aging
4. At age 50, all the measures show very strong toxin-dose response.

⇒ Cumulative damage impairs ability to adapt

“Unconventional” Laboratory Tests

- Challenge testing
- Hair analysis
- Direct measures of POPs in blood, urine, adipose tissue
Evaluation of Metal Exposure – Provocation

- Provocation – the use of a chelating agent – before urine collection often done clinically, but several limitations
  - No “official” reference range for provoked urine
  - Most chelating agents do not extract metals from all tissues, thus does not necessarily represent total body burden
    - Example: Brain is one of the main target organs for both elemental and organic mercury, yet agents do not chelate brain mercury
- Despite limitations, widely used and advocated by clinicians, in part, to see efficacy of chelating agent as a guide to treatment, and based on empirical evidence

Rooney JP. The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. Toxicology. 2007
Is Challenge Testing Valid?

- Poor correlations of standard tests for mercury
- Unpublished research from corporate wellness project
- Published amalgam number correlation
- Published fish consumption correlation
What We Found In Canada

- Deviations from the mean of 14%, 29% and 91% respectively
- DMPS is spreading distribution, suggesting that it is better at differentiating mercury body load
- Some VERY high
Hg Assessment Correlations

- Extensive measurements in 65
  - Whole blood Hg
  - Oral DMPS challenge
  - Amalgam surfaces

- Correlations
  - Whole blood w pre urine: $r = 0.40$
  - Whole blood w post urine: $r = 0.57$
  - Pre urine w post urine: $r = 0.68$
  - Amalgams w pre urine: $r = 0.26$
  - Amalgams w whole blood: $r = 0.36$
  - Amalgams with post urine: 0.44

- Clear documentation that challenge testing is better
Modest Correlation with # of Fillings

- Very large study
- Surprisingly only reported none versus 1 or more fillings
- Huge overlap!
- Not controlled for fish consumption

Strong Correlation with Fish Consumption

- Compared 0 to 1-2 to 3 or more servings per week
- First urine showed essentially no differentiation
- Challenge testing showed clear correlation
- Still a lot of variation

Cadmium

- Blood cadmium - a marker of current exposure but may also reflect body burden from long-term retention of cadmium in the liver and kidney
  - Assessed as whole blood
- **Urinary cadmium is thought to more specifically be a marker of cumulative exposure**

Arsenic Evaluation

- Blood arsenic not a good marker for long term exposure
- May not be a sensitive marker for acute exposure
- Urinary arsenic used as a marker for acute exposure
  - Variety of arsenic compounds in urine, may reflect toxicity
- Urinary levels also used for chronic exposure, but may only be relevant if exposure has stayed constant (and still present)
- Other tissues (hair, nails) may reflect chronic exposure
  - Hair & toenails do reflect past exposure, but susceptible to external contamination and lack standard ranges

Toxic Metal Assessment Recommendation

- Acute exposure
  - First morning urine
- Body load
  - 300 mg DMPS (Hg) + 500 mg DMSA (Pb, Hg, Cd)
  - 6 hour collection
- 50 yo Japanese man
- Smoked and ate a lot of sushi
- Did not follow advice
- Cancer 2 years later
POPs – Laboratory Tests

• Urine, blood, adipose tissue and breath
• Can be directly measured, but expensive and only a few of the about 100 most important of the thousands in the environment
Directly Measure POPs and Solvents

Environmental Pollutants Profile

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Result</th>
<th>Units</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylene Exposure 3-Methylhippurate</td>
<td>0.39</td>
<td>µg/g Cr</td>
<td>&lt; 0.33</td>
</tr>
<tr>
<td>2-Methylhippurate</td>
<td>5.62</td>
<td>µg/g Cr</td>
<td>&lt; 5.67</td>
</tr>
<tr>
<td>Toluene Exposure Hippurate</td>
<td>161</td>
<td>µg/mg Cr</td>
<td>&lt; 644</td>
</tr>
<tr>
<td>Benzoate</td>
<td>&lt; 0.01</td>
<td>µg/g Cr</td>
<td>&lt; 0.49</td>
</tr>
<tr>
<td>Benzene Exposure Malonic Acid</td>
<td>0.04</td>
<td>µg/g Cr</td>
<td>&lt; 0.13</td>
</tr>
<tr>
<td>Trimethylbenzene Exposure 3,4-Dimethylhippurate</td>
<td>0.06</td>
<td>µg/g Cr</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Styrene Exposure Mandelate</td>
<td>0.17</td>
<td>µg/g Cr</td>
<td>&lt; 0.24</td>
</tr>
<tr>
<td>Phenylglyoxylate</td>
<td>0.22</td>
<td>µg/g Cr</td>
<td>&lt; 0.39</td>
</tr>
<tr>
<td>Mandelate + Phenylglyoxylate</td>
<td>0.39</td>
<td>µg/g Cr</td>
<td>&lt; 0.64</td>
</tr>
<tr>
<td>Phthalate Exposure Monoethyl Phthalate</td>
<td>&lt; 0.01</td>
<td>µg/g Cr</td>
<td>&lt; 0.06</td>
</tr>
<tr>
<td>Phthalic Acid</td>
<td>0.04</td>
<td>µg/g Cr</td>
<td>&lt; 0.25</td>
</tr>
<tr>
<td>Quinolinate</td>
<td>1.92</td>
<td>µg/mg Cr</td>
<td>&lt; 5.53</td>
</tr>
<tr>
<td>Paraben Exposure Para-Hydroxybenzoate</td>
<td>1.63</td>
<td>µg/g Cr</td>
<td>&lt; 2.73</td>
</tr>
</tbody>
</table>
Monitoring -- 8-OHdG

- Oxidized nucleoside
- Direct measure of DNA damage
- Indirect measure of oxidative stress and toxin load
- Correlates with:
  - Multiple cancers
  - Mitochondrial damage
  - Rate of aging
  - Smoking
  - Etc.
8-OHdG Correlates with Pack-Years of Smoking

8-OHdG Correlates with Mercury

Summary Assessment

Body chemical load:
- GGT: > 25
- Uric acid: > 5.0 mg/dl
- ALT: >30 U/L
- Bilirubin: >0.8 mg/dl
- CBC: < 6,000
- Platelet: < 250,000

Total/Monitor:
- 8-OHdG: >4

Metal body load:
- First urine for current exposure
- Cd (?), Hg, Pb:
  - Oral:
    - DMPS: 300 mg
    - DMSA: 500 mg
  - Collect urine for 6 hours
- As: hair or nails
- Cd: urine