Educational Case

Educational Case: Lead Poisoning

Academic Pathology
Volume 4: 1–3

DOI: 10.1177/2374289517700160
journals.sagepub.com/home/apc

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, environmental mechanisms, occupational exposure, lead poisoning, cell injury

Received January 12, 2017. Received revised February 16, 2017. Accepted for publication February 21, 2017.

Primary Objective

EM1.5: Occupational Exposure. Provide examples of industrial, occupational, or environmental exposures that produce disease, the resultant pathologic changes in these affected organs from chronic exposure, and indicate what organ systems are most commonly affected by which agents.

Competency 1: Disease Mechanisms and Processes; Topic EM: Environmental Mechanisms; Learning Goal EM1: Cell Injury.

Patient Presentation

A 7-year-old boy is brought to the clinic by his mother with complaints of increased irritability, vague abdominal pain, and constipation. The child had been well until these vague symptoms began approximately 6 months earlier, and these symptoms are becoming more frequent. The school has informed the parents that their child has difficulty paying attention in class over that past few months. The family lives in an inner-city home. The child has 3 younger siblings.

On physical examination, the child appears well developed and well nourished. He is in the 40th percentile for height and weight. He had measured in the 50th percentile 1 year ago. He is alert and oriented. He has mild tenderness elicited by abdominal palpation; the remaining examination is unremarkable.

Diagnostic Findings

Complete blood count (CBC) is given in Table 1.

Questions/Discussion Points

Given the Clinical History, What Is a Broad Differential Diagnosis?

The differential diagnoses include attention-deficit disorder, lead toxicity, iron deficiency anemia, fetal alcohol syndrome, thyroid disorder, hypercalcemia, and pituitary disorders. One could also consider vision or hearing impairments. The CBC findings will help narrow this differential.

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Table 1. Complete Blood Count.

Hematocrit	28%
Hemoglobin	8 g/dL
WBC	5300/mm^3
Neutrophils, segmented	65%
Eosinophils	2%
Lymphocytes	25%
Monocytes	8%
Platelet count	150 000/mm^3

Note. Microscopic Review Reveals Microcytic Hypochromic Anemia With Basophilic Stippling.
Abbreviation: WBC, white blood cells.

What Is the Most Likely Diagnosis in This Child?

With the behavioral changes, irritability, vague abdominal complaints, decreased growth, and microcytic hypochromic anemia with basophilic stippling, lead toxicity must be considered very high in the differential diagnosis. This can be confirmed with laboratory testing. In our patient, 32 μg/dL of lead was found in the blood. As early detection can be subtle, constant vigilance of the primary care provider is necessary. It is important when patients present with attention-deficit disorders to be sure to rule out organic causes.

What Are the Risk Factors for Lead Poisoning?

There are multiple environmental risk factors for lead poisoning. Leaded gasoline was banned in the United States in 1996, but deposits may still be found in the soil. The amount of lead allowed in decorative paints intended for household use was markedly reduced in the United States as of 1978.[1] Lead is still used in many other products. These can include imported items such as toys, furniture, ceramics, crystal ware, "traditional" medicines, and spices. Even cosmetics may contain variable amounts of lead. Occupational exposure from employment in mining, metallurgy, construction, battery manufacture, and recycling can contaminate the clothes of employees who may inadvertently bring lead containing dust home. Recent events have highlighted the dangers of lead pipes for water or copper pipes that have lead soldering which can leak lead into drinking water. High levels of lead have also been found when certain ceramics are used that have a lead-based paint or glaze, especially products from Mexico or China. Other less common risk factors include artists making stained glass artifacts or windows, as this requires lead soldering.

What Are Acceptable Levels of Lead?

In 2012, the Centers for Disease Control (CDC) chose 5 μg/dL[2,3] as the reference level at which clinical intervention should be taken to limit additional exposure to lead. It is important to note that it is not a toxicologic threshold, as no safe blood lead level has been determined. This level identifies the 2.5% of children with the highest blood lead levels based on US survey data collected prior to that year. More recent survey data have found that the value for this cutoff has dropped to ~4 μg/dL. Ultimately, the CDC will continue to adjust the value of this cutoff as new epidemiologic data become available. Interventions to prevent further lead accumulation, which are also appropriate as measures to prevent lead poisoning from initially occurring, include identifying and eliminating the sources of exposure, changing the behavior that leads to ingestion of lead-containing materials (nonnutritive hand/mouth activity), and the correction of any nutritional deficiencies, particularly those of calcium, iron, and vitamin D.[4] Chelation therapy (drugs to enhance a lead diuresis) may be added if blood lead levels above 45 μg/dL are found.

How Can You Make a Diagnosis of Lead Poisoning?

Anemia often is observed in young lead-poisoned children. One should remember that a microcytic, hypochromic anemia will most often be found in patients with iron deficiency anemia or alpha-thalassemia. Examination of a blood smear looking for basophilic stippling may be very useful to separate the causes of anemia in some patients. The confirmation is made by obtaining a blood lead level as described earlier.

What Organ Systems Can Be Involved With This Disorder?

Lead toxicity can affect multiple organ systems at the biochemical, subclinical, and clinical levels. The findings are related to the blood lead level. At the biochemical level, toxicity to many enzymes has been documented. As the level of lead in the blood rises over 10 μg/dL, the levels of 1,25-dihydroxyvitamin D fall. This is the active hormonal form of vitamin D and is necessary for efficient intestinal absorption of calcium. Three of the 8 enzymes necessary for heme production are inhibited by lead, beginning at levels as low as 10 μg/dL for the most sensitive enzyme, delta-aminolevulinic acid dehydratase. When the last enzyme in the pathway, ferrochelatase, is impaired, the precursor molecule protoporphyrin accumulates in the cell. Measurement of erythrocyte protoporphyrin levels in peripheral blood samples may be a useful clinical tool for following toxicity in patients with lead levels over 20 μg/dL. In studies of children, cognitive scores, hearing, and growth have all been found to be inversely related to blood lead levels. However, at lower lead levels, these would be subclinical findings, that is, not presenting with symptoms. At higher levels, >20 μg/dL, lead can be associated with chronic or recurrent abdominal pain and constipation, loss of appetite, attention deficits, and hyperactivity. In rare cases, peripheral nerves may be impaired, resulting in weakness of the arms and legs, but this is more typically seen in adults with chronic severe lead poisoning. Chronic lead poisoning may uncommonly be associated with a "lead line" in the mouth: This is a line of hyperpigmentation on the gingiva adjacent to the teeth. At much higher levels of lead, over 100 μg/dL, encephalopathy and death can occur. One may have acute poisoning from very high levels of lead exposure, but much more common are the chronic lower levels of exposure

to lead. The skeletal system may show increased radiodensities at the ends of the long bones at the metaphyses. The renal system may show chronic tubulointerstitial disease over time with high lead levels. Adults with chronic lead exposure may show demyelination of the peripheral nerves.

How Would You Describe the Changes Seen in the Blood Smear of a Patient With Lead Poisoning?

One of the more common systems involved with lead poisoning is the hematologic system where one can find anemia, red blood cells with basophilic stippling (which is one of the hallmarks of diagnosis), and ring sideroblasts on bone marrow evaluation. The anemia most often found is a microcytic, hypochromic anemia, but this is likely due to other causes such as iron deficiency. The mechanism of the ring sideroblasts is related to the accumulation of iron-laden mitochondria in the red blood cell precursors due to the inhibition of ferrochelatase by lead.

What Is the Mechanism of Lead Poisoning?

Lead is a heavy metal that binds to proteins potentially altering their function. It competes with essential metals such as calcium for binding sites. In test tube studies, many calcium-binding proteins have a higher affinity for lead than calcium. These can result in multiple effects. For example, neurotransmitter release is a calcium-dependent process perturbed by the presence of lead. In children, over 70% of retained lead resides in the skeleton from which it can be released very slowly over years to decades after cessation of further ingestion.

Is Lead Absorption the Same for Children and Adults?

No. Lead compounds are poorly dissolvable in water. Lead absorption is dependent on the gut's ability to digest lead-containing material; this is enhanced in acidic environments like the stomach. Like calcium, lead is absorbed more efficiently in children than adults. In children, over 50% of the digested lead (lead in solution) can be absorbed via the intestinal tract compared to 15% in adults.

What Are Possible Treatments of Lead Poisoning?

For acute ingestion, a gastric lavage could be performed to decrease the amount of lead-containing objects still in the stomach. Cathartics can be given to rapidly remove lead already further into the intestinal tract. For chronic ingestion, chelation therapy may be necessary for lead levels of $\geq$45 μg/dL as per CDC/American Academy of Pediatrics (AAP) recommendations. Treatment successfully improves biochemical profiles; however, less data support the reversibility of neurocognitive effects of lead. In all cases of increased lead levels, treatment should include identification and elimination of the source of the lead, behavior modification to limit ingestion, and nutrition maximization.

Teaching Points

- Low lead levels, under 10 μg/dL, can have permanent neurologic effects in children, especially contributing to attention deficit disorders and decreased cognitive abilities.
- Higher lead levels can affect multiple organs such as its long-term accumulation and retention (over years) in bone and teeth while causing toxicity in the bone marrow with shortened red cell survival and the development of microcytic hypochromic anemia with basophilic stippling; central nervous system complaints of difficulty learning and focusing; decreased renal function; and gastrointestinal complaints of abdominal pain and constipation.
- Chronic low levels of exposure are much more common than acute high levels of toxicity.
- A high degree of vigilance is required to suspect lead toxicity, especially in children where absorption of lead is higher than in adults.
- Risk factors for lead toxicity include the ingestion of environmental sources of lead such as in drinking water, lead paint or the dust derived from that paint, contaminated soil as well as secondary exposure from occupational hazards such as workers from foundries, paint manufacture, or battery factories.
- The mechanism of lead poisoning centers around its affinity for proteins and its competitiveness with essential metals to protein-binding sites.

Authors' Note

The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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