Lead Toxicity in the Pediatric Patient with Sickle Cell Disease: Unique Risks and Management

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ABSTRACT

Lead toxicity is the result of lead ingestion, one of the most common ingestions in the pediatric population. Nationwide and statewide efforts to recognize and curtail this epidemic have led to declining rates of toxicity. In patients with sickle cell disease (SCD), lead toxicity can be an elusive diagnosis due to overlapping symptom profiles, and inconsistent follow-up with a primary care physician can make the diagnosis even more difficult. In this article, two illustrative cases of lead toxicity in patients with SCD are described. The discussion reviews the current risk factors, screening, and inpatient management of lead toxicity, as well as describing the unique and sometimes confounding presentations of lead toxicity versus sickle cell crisis. [Pediatr Ann. 2018;47(1):e36-e40.]

The harmful effects of childhood lead exposure and poisoning have been well characterized and described in the literature, but there continues to be acute and chronic lead exposure in our most vulnerable pediatric population.1 Despite statewide, national, and international efforts, lead toxicity still accounts for 0.6% of global disease burden according to the World Health Organization.1 This article describes two patients with sickle cell disease (SCD) who present with lead toxicity. Although the co-existence of these two diseases (SCD and lead toxicity) has been recorded infrequently, the SCD population possesses unique risk factors that may influence management and early diagnosis of lead toxicity.

ILLUSTRATIVE CASE 1

The patient was a 2-year-old girl with a history of SCD previously complicated by acute chest syndrome and aplastic crisis requiring transfusions who presented to the emergency department (ED) with an elevated lead level. Two weeks prior to presentation, the patient was found to have a blood lead level (BLL) of 35 mcg/dL and was prescribed oral succimer by her primary care physician (PCP). Three days prior to her presentation to the ED, a repeat test showed a BLL of 69 mcg/dL. At this point, the PCP recommended hospital admission for inpatient monitoring and chelation, especially because there was some concern regarding compliance.

Of note, the patient lived in a house built before 1975 with concern for lead paint on the windowsills, a situation that was addressed by the landlord (windowsills were repainted 1 week prior to the patient’s presentation). Her PCP noted that the patient also exhibited pica for paper, with frequent hand to mouth activity. She also had a history of constipation and had been recently prescribed a laxative (polyethylene glycol). Otherwise, her mother had not noticed any changes in appetite or activity and a review of the rest of her systems was negative, including neurological (no headaches, confusion, dizziness, weakness) and other gastrointestinal (no diarrhea, vomiting, abdominal pain) symptoms.

During the patient’s admission, she continued her treatment with oral succimer and home medications for her SCD (hydroxyurea and penicillin) until a follow-up BLL test showed a value of 71 mcg/dL. Because her BLL was >65 mcg/dL, Poison Control recommended initiating ethylenediaminetetraacetic acid (EDTA). Two doses of calcium EDTA were administered on the second day of admission, with a subsequent drop of BLL to 46 mcg/dL. After receiving EDTA, her activity level as well as her stool output increased (perhaps resolving her constipation).
both likely from a decreasing BLL. She was discharged with instructions to continue taking the oral succimer (3 doses/day) and maintain close follow-up with her PCP.

She completed oral chelation and her BLL improved, at which point her chelation therapy was discontinued.

**ILLUSTRATIVE CASE 2**

The patient was a 4-year-old girl with a history of SCD previously complicated by vaso-occlusive crises (VOC) who initially presented with several days of intermittent, colicky abdominal pain with associated nausea and vomiting. She was initially examined at an outside hospital for appendicitis, which was negative, and discharged home with an oral pain regimen. A few days later, the patient presented again to our institution with worsening abdominal pain and an episode of bilious emesis, and was subsequently admitted for pain control.

On admission, the patient’s abdominal pain remained refractory to oral pain medications, ultimately requiring a continuous morphine patient-controlled analgesia pump. Despite an increase in her pain regimen, and fluid and blood product administration, the patient continued to have hypertension (160/100 mm Hg) and tachycardia (170-190 beats per minute). She also received enemas, which yielded small hard stools and only mild improvement of her pain. A kidney, ureter, and bladder X-ray study confirmed constipation, with dilated loops of bowel and copious stool. The working diagnosis at this point was constipation versus an atypical VOC. Due to her refractory hypertension and tachycardia, she was ultimately managed in the pediatric intensive care unit, receiving hydralazine for management of her high blood pressure.

Of note, the patient had a 2-week history of pica, ingesting stuffing from couch cushions and paint chips. Also, at her PCP appointment 2 weeks prior to her presentation, she was noted to have an elevated BLL of 11.9 mcg/dL. Due to the severity of her pica, a test for lead level was sent, which came back at 120 mcg/dL.

Dimercaprol (British anti-Lewisite) and calcium EDTA were both initiated based on recommendations from poison control. Lead levels on subsequent days were 116, 74, 33, and 34 mcg/dL. Much like the previous case, the patient’s home was inspected by the Department of Public Health. Recommendations were made for remodeling and repainting due to lead in the basement. The patient was discharged on oral succimer, and initially resided at a relative’s house until her home underwent necessary lead removal. She was followed closely by her PCP, with eventual decrease and resolution of her elevated BLL.

**RISK FACTORS**

Younger children (<6 years) are especially susceptible to the toxic effects of lead. They have incomplete blood-brain barrier allows for increased lead penetration, leading to greater deficits on the developing brain. Developmentally appropriate oral exploration and behaviors promote greater ingestion of lead-containing substances. In addition, younger children are more susceptible to iron-deficiency anemia, which in itself can lead to increased absorption of lead in the gastrointestinal tract.

In addition to this unique physiology, environmental effects play an equally important role. The highest risk of lead toxicity occurs in ethnic minorities who are living in economically disadvantaged neighborhoods. Black children are 3 times more likely and Hispanic children 2 times as likely to have elevated BLL compared to white children. Children residing in older homes (built before 1970) and rental units are also at increased risk.

**SCREENING**

The current Bright Futures/American Academy of Pediatrics periodicity schedule recommends risk assessments at well-child visits (ages 6 months, 9 months, 12 months, 18 months, 24 months, 3 years, 4 years, 5 years, and 6 years) and, if positive, obtaining BLL. In Illinois, state Medicaid requires universal BLL testing at the 12-month and 24-month visits, and in Chicago, where all children are considered to live in a high-risk zip code, BLLs should be obtained at ages 6, 12, 18, 24, and 36 months (or alternatively ages 9, 15, 24, and 36 months). Table 1 provides guidelines for targeted screening.

For children with SCD, an additional consideration is the unusually high prevalence of pica. Pica is the repeated and compulsive ingestion of non-nutritive substances inappropriate for patient’s developmental stage. Classically, pica has been associated with iron-deficiency anemia and lead encephalopathy, but because of the independent association of SCD and pica, more frequent surveillance for both pica and BLL in the SCD population may be warranted. Data from review articles suggest annual BLL screening of children of all ages with SCD due to the uniquely high prevalence of dysfunctional eating patterns that persist into older age.

**DIAGNOSIS AND TESTING FOR LEAD TOXICITY**

There is no established lower limit of BLL in lead toxicity, and each child with high BLLs should be followed closely. Most patients with an elevated BLL are asymptomatic with mild deficits in neurocognitive function that
are usually discovered during routine screening. Symptomatic lead toxicity can manifest in a variety of ways, commonly affecting four major systems: nervous, hematological, renal, and gastrointestinal (Figure 1). Multisystem involvement and similar symptom profile of lead toxicity and VOCs in patients with SCD can delay diagnoses and lead to unfavorable outcomes. Although symptomatic lead toxicity in SCD is uncommon, awareness and differential diagnoses that include lead toxicity are imperative. Diagnoses of VOC and lead toxicity are both serious, but delays in diagnosing lead toxicity can progress rapidly to lead encephalopathy, especially in children. Early vague complaints followed by rapid deterioration are common in SCD patients with lead toxicity. Table 2 summarizes key differences between lead toxicity in the general and SCD populations.

**Nervous System**
Detectable BLLs are associated with irreversible neurocognitive deficits that persist into adulthood. Mild impairment from low lead exposure includes decreased learning, memory, verbal ability, and early signs of attention-deficit/hyperactivity disorder. Moderate exposure can lead to increased irritability and lethargy. Acute encephalopathy occurs when BLL is >100 mcg, and is characterized by acute vomiting, altered

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### Table 1.
**Targeted Screening Guidelines for Lead**

- Does your child live in or regularly visit a house with peeling or chipping paint built before 1960?
- Does your child live in or regularly visit a house built before 1970 with recent or ongoing renovation or remodeling?
- Does your child have a sibling or playmate being treated for lead poisoning?
- Does your child live with an adult whose job or hobby involves exposure to lead?
- Does your child live near an active lead smelter, battery recycling plant, or other industry likely to release lead?

### Table 2.
**Key Differences Between Lead Toxicity in the General and SCD Populations**

- Older mean age: in a systematic review, the mean age of coexisting SCD and lead toxicity was age 5 years compared to 18-36 months in the general population.
- Higher incidence of pica: a review noted a pica history in 76% of the SCD population.
- Prominent chief complaints in SCD patients ultimately diagnosed with lead toxicity were abdominal pain and limb pain; in most cases these symptoms were initially attributed to VOCs.
- There have been reports that suggest greater vulnerability of SCD population to lead toxicity with a number of theories as to why:
  - SCD patients have greater incidence of zinc deficiency with robust animal models showing increased absorption of lead with zinc deficiency in the GI tract.
  - Renal insufficiency causing impairment of lead excretion.

Abbreviations: GI, gastrointestinal; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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![Figure 1. Symptomatic lead toxicity can manifest in a variety of ways. ADHD, attention-deficit/hyperactivity disorder. From the Centers for Disease Control and Prevention (in the public domain; permission is not required).](image-url)
levels of consciousness, seizures, or coma. Lead encephalopathy can progress very rapidly, especially in the SCD population, potentially due to delayed diagnosis and increased susceptibility to lead. Interestingly, although peripheral neuropathy is rare in children with lead toxicity, children with sickle cell anemia have a higher incidence and seem to be predisposed to peripheral nerve damage at high BLLs.

The most common presentations of lead neuropathy in SCD patients are foot and wrist drop.

**Gastrointestinal**

Gastrointestinal symptoms of lead toxicity are often vague and include sporadic vomiting, abdominal pain, and constipation. Although in the SCD population complaints of abdominal pain are often attributed to VOCs, it is prudent to keep lead toxicity in the differential diagnosis due to similar symptom profiles. There have been multiple case reports showing abdominal pain mistakenly attributed to VOC in the setting of severe lead toxicity, with subsequent delay in treatment and in certain cases progression to lead encephalopathy.

**Hematology**

High BLLs can independently cause decreased hemoglobin synthesis (due to interruption of the heme pathway), and acutely high BLLs can cause hemolysis. However, more often, iron deficiency and lead toxicity are coexistent and synergistic in causing a microcytic anemia. In patients with iron deficiency there is increased lead absorption, and in patients with high lead levels there is decreased iron absorption. Iron deficiency is usually uncommon in the SCD population (due to increased gastrointestinal absorption of iron associated with hemolysis and intermittent transfusions), but when it occurs, is associated with malnutrition.

**Renal**

Prolonged and high levels of lead can lead to histologic chronic interstitial nephritis. Lead levels as low as 10 mcg/dL can affect renal function. Clinically significant renal disease is manifested with a Fanconi-type syndrome with glucosuria, aminoaciduria, and renal phosphate wasting. In the SCD population in particular, there is a higher incidence of hyponatremia from syndrome of inappropriate antidiuretic hormone secretion.

**Bones and Teeth**

Radiologic imaging of long bones is not part of diagnostic testing and neither are testing of hair/teeth/fingernails for lead or searching for gingival lead lines.

**INPATIENT TREATMENT**

Once diagnosed, the treatment of lead toxicity is the same for the general and SCD population. If a BLL is found to be >70 mcg/dL or if a patient is symptomatic with a BLL >45 mcg/dL, the patient must be hospitalized for combination chelation therapy. The options for chelation therapy are listed in Table 3.

**TABLE 3. Options for Chelation Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Blood Lead Level (mcg/dL)</th>
<th>Mechanism</th>
<th>Administration</th>
<th>Side Effects</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimercaprol (British anti-Lewisite)</td>
<td>&gt;70</td>
<td>Increases urinary excretion</td>
<td>Deep intramuscular</td>
<td>Prolonged PTT, Hemolysis, Hepatotoxicity, Contraindicated in patients with peanut allergy</td>
<td>25 mg/kg divided 6 doses/day for 3 days</td>
</tr>
<tr>
<td>Calcium EDTA</td>
<td>&gt;70</td>
<td>Increases urinary excretion</td>
<td>Intravenous</td>
<td>Nephrotoxicity</td>
<td>50 mg/kg per dose, continuous infusion in normal saline/DSW (max dose 1 g/day) for 5 days</td>
</tr>
<tr>
<td>Succimer</td>
<td>&gt;45</td>
<td>Increases urinary excretion</td>
<td>Oral</td>
<td>Transient rash, Transient elevation in LFTs, Neutropenia, Abdominal cramping, Strong sulfur odor</td>
<td>Total of 19 days, 10 mg/kg TID for first 5 days, then BID for the next 14 days</td>
</tr>
</tbody>
</table>

Abbreviations: BID, two times daily; D5W, 5% dextrose in water; EDTA, ethylenediaminetetraacetic acid; LFTs, liver function tests; max, maximum; PTT, partial thromboplastin time; TID, three times daily. Adapted from the Illinois Department of Public Health.

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Centers for Disease Control and Prevention (CDC) suggests dual therapy with succimer and EDTA.3

Once admitted, the provider should contact poison control, the state public health department, early intervention (specialized services provided by the state targeting developmental delay and disability), and notify the patient’s PCP. The public health department will inspect the home for lead exposures and help eliminate risk of further exposure. Siblings should also be tested for lead toxicity.

CARE AFTER DISCHARGE
At the end of a treatment cycle (19 days of succimer, 3 times daily), BLL will usually have declined to <25 mcg/dL. After discharge, BLLs should be measured weekly to ensure there are no repeat exposures. If BLL rebounds to >80% of the original lead level and is >45 mcg/dL, the child will need to be hospitalized for retreatment.3 If BLLs continue to be stable, these visits can be spaced out, but current recommendations2 suggest visits every month for at least 4 to 6 months. Early intervention should be consulted for all children affected by lead toxicity regardless of neurocognitive and developmental deficits. Lastly, a child should not be discharged without ensuring a lead-free environment to live in, which can be established with help from social work services and a state’s public health office.

CONCLUSION
Lead toxicity in the SCD population can look deceptively similar to VOC, presenting most often with vague abdominal pain or localized limb pain. It is especially important to diligently screen for lead based on the recommendations from the state as well as the CDC, perhaps even more often in SCD patients who have a high incidence of pica behavior. Finally, keeping lead toxicity in the differential diagnosis can potentially prevent the rapid progression of lead encephalopathy and delays in treatment.

REFERENCES