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Children With Autism Spectrum Disorder and Lead Poisoning: Diagnostic Challenges and Management Complexities

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Introduction

Exposure of children to lead in their environment continues to be an enormous public health issue, global in scope. As many as 500 000 children ages 1 to 5 years in the United States have blood lead levels (BLL) above the reference value set by the Centers for Disease Control and Prevention (CDC).¹ Autism spectrum disorder (ASD) is another major health concern with the prevalence increasing from about 1 in 150 children age 8 years in 2000 to 1 in 68 children age 8 years in 2012.^{2,3} These 2 childhood conditions together exact an enormous societal toll in terms of suffering and lost productivity. Bellinger⁴ estimated that 22 947 450 full-scale IQ point losses can be attributed to childhood lead poisoning and 7 109 899 full-scale IQ point losses can be attributed to ASD in children age 0 to 5 years in the United States.

A number of studies have explored the relationship between ASD and lead exposure.⁵⁻⁷ Shannon and Graef⁶ described a case series of 17 children with both lead poisoning and pervasive developmental disorders (PDDs) or autism. In another study, children with ASD were found to have significantly higher BLL than their siblings without ASD.⁵ A population-based study of older children with autism living in Alberta, Canada, found elevated BLL in some of these children.⁸ One twin study using matrix markers from shed baby teeth found differences in the deposition of metals during late pregnancy and early

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Author Contributions

ADW conceptualized and designed the study, assisted in analyzing and interpreting the data, drafted the initial manuscript, assisted in collection and assembly of the article, participated in critical revision of the article for important intellectual content. MH assisted in analyzing and interpreting the data and prior literature, assisted in drafting the article, provided administrative and logistical support for the study, participated in critical revision of the article for important intellectual content. BS assisted in analyzing and interpreting the data and background research articles, assisted in drafting the article, participated in critical revision of the article for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Authors' Note

The content of this review article is meant for education purposes only. Decisions about evaluation and treatment are the responsibility of the treating clinician and should always be tailored to individual clinical circumstances.

Declaration of Conflicting Interests

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post-natal life between children who later developed ASD and their twin who did not.⁹ With evidence of such associations, researchers have called for prospective longitudinal studies into the relationship between environmental lead exposure and behaviors typical of autism.¹⁰

Published reviews on the management of ASD often advise health care providers to monitor children with ASD and pica behaviors for elevated BLL.¹¹⁻¹⁴ However, there is scant literature providing guidance to health care providers regarding how often to conduct such surveillance or how to medically manage children with both ASD and an elevated BLL. In this review, we offer recommendations to clinicians drawing on recently published guidance as well as our own experience caring for families of children suffering from both conditions.

Neurotoxicity of Lead

Lead is a known neurotoxin, able to produce metabolic and infrastructural perturbations at the molecular and cellular levels of the developing nervous system.¹⁵ Children are much more susceptible to the adverse neurodevelopmental effects of lead than are adults, due to the vulnerability of their nervous system, the postnatal continuation of nervous system maturation, and the increased permeability of neuronal structures to lead's entry.¹⁵ Numerous studies have confirmed adverse neurodevelopmental, neurobehavioral, and cognitive effects of prenatal and postnatal lead exposure.^{16,17} Prospective longitudinal studies have demonstrated the long-lasting sequelae of lead exposure on intellectual and academic achievement later in childhood even after apparently low-level exposures with BLL less than 10 µg/dL.¹⁸⁻²⁰ Neurological outcomes include cognitive damage, hearing loss, visual effects, delayed speech acquisition, learning disabilities, lower reading and arithmetic skills, poor attention, deficits of other aspects of executive function, and other educational, behavioral, and emotional problems, which can persist into adolescence and adulthood.^{19,21-29}

Overlapping Conditions: Lead Poisoning and ASD

Symptoms of ASD share some similar characteristics to the symptoms of lead neurotoxicity noted above.⁷ For example, *DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition)* criteria for ASD, as detailed by the American Psychiatric Association, includes persistent deficits in social-emotional reciprocity and nonverbal communicative behaviors.³⁰ Significant language delay and coexisting intellectual disability are notable in many children with ASD.³¹ In addition to neurologic and behavioral symptoms, both childhood lead poisoning and ASD are often associated with poor appetite, restricted food choices, and gastrointestinal symptoms, such as constipation or abdominal discomfort.

These similarities may prompt parents and clinicians to wonder whether lead poisoning in a child can cause ASD, and if there might, therefore, be a treatable cause of their child's ASD. However, current scientific evidence does not support this hypothesis. Instead, any association of ASD and lead poisoning is more likely secondary to pica habits, the compulsive chewing and eating of nonfood items, seen commonly in children with ASD. This behavior puts them at high risk for exposure to lead-containing dust and other lead-contaminated objects. The association between such pica behaviors and a higher risk of lead poisoning was described as early as 1976 by Cohen et al.⁵ Another study confirmed that

children with ASD are more likely to be re-exposed to sources of lead contamination than children without ASD.⁶ Unfortunately, the normal hand-mouth behaviors and oral exploratory habits of infancy, which usually extinguish within the preschool years, can persist in children with ASD well into later childhood and beyond such that their risk for lead contamination continues. While these pica behaviors continue, these children also continue to grow taller and stronger, allowing them access to new surfaces and areas of households that may contain lead hazards not previously accessible to them at a younger age. A study that investigated epidemiologic characteristics of severe lead poisoning in New York City found a trend toward severe lead poisoning occurring at older ages in children with ASD compared with the cases without ASD (5.99 years vs 3.69 years, respectively).³²

Diagnosis

Misdiagnosis

Despite some overlapping symptoms, there is no convincing evidence that childhood lead poisoning causes ASD; however, rare cases of misdiagnosis can occur. For example, a case was reported in which a child misdiagnosed with severe autism was found, instead, to suffer from chronic lead poisoning. His hearing improved, with accompanying advancement in neurodevelopmental status (receptive and expressive language), after his very severe lead poisoning was treated successfully with chelation.⁵ The risk of lead poisoning in genetic disorders similar to autism, such as Landau-Kleffner syndrome, has also been reported.³³

Lead poisoning may manifest in a number of different ways in a child with ASD. Although potentially asymptomatic, a child may also become more irritable secondary to abdominal colic from lead. While becoming quiet and more withdrawn may seem like an improvement in the behavior of a child with autism and attention-deficit/hyperactivity disorder, this may actually be the unrecognized beginning of lead-induced encephalopathy, a medical emergency.³⁴ Clinicians should maintain a high level of suspicion for lead poisoning in children with ASD when such symptoms arise.

ASD Risk Factors for Exposure to Lead

Pica behaviors predispose children with ASD to unrecognized foreign body ingestion, which poses an additional risk if the foreign body contains lead-leaching materials. Pica also predisposes children to ingestion of other nonfood items that may be contaminated with lead such as dirt, house dust, and paint chips. Because of their restricted diets and related nutritional deficiencies, children with ASD may be iron deficient, a known comorbidity of lead poisoning.³⁵ As evidenced by mouse studies, the presence of iron deficiency may enhance gastrointestinal uptake of lead, predisposing those with lead exposure to elevated blood lead levels.³⁶

Routine Screening and BLL Testing

Providers should be aware of the recommended universal or targeted lead screening guidelines in their locality and, at a minimum, adhere to these guidelines. Most children with ASD will require enhanced and extended monitoring for lead poisoning. Table 1 offers some

recommendations to clinicians regarding screening and diagnosis of lead poisoning in children with ASD.

Some parents take their children to alternative health care providers for assessment of their ASD. These providers may send hair and/or urine for analysis of metals. Hair is a complex medium that is technically difficult to assay with precision. The interpretation of levels of metals found to be elevated in such an analysis has been challenged.³⁷ Hair analyses have been shown to be unreliable when performed in commercial laboratories.^{38,39} Children with reports of elevated hair lead levels often have very low BLLs, no evidence of exposure to environmental lead, and no need for medical management. In such cases a venous BLL can be obtained to determine the child's actual lead burden.

Management

Table 2 lists some key features of children suffering from both an elevated BLL and ASD. The complexity of the medical needs of the child with both ASD and an elevated BLL demands a thoughtful, comprehensive, coordinated, and multidisciplinary approach to their care. Social, educational, economic, housing, and occupational challenges confront their parents and guardians. The coordinated team approach often includes involvement of a variety of professionals: physicians and nurse practitioners, developmental specialists, nurses, physical and occupational specialists, pharmacists, social workers, case managers, state and local public health workers, private housing inspectors, certified lead abatement firms and remodeling construction specialists, plumbers, landlords, bankers and/or loan agency staff, teachers and school officials, daycare workers, and other community-level professionals. Primary care providers and developmental medicine specialists often must act as a coordinator of these important resources and advocate on behalf of the family. Below are some special considerations that warrant attention in treating children with ASD and lead poisoning.

Outpatient Management

Children with lead poisoning require close medical monitoring with frequent office visits and even occasional emergency department referrals. Table 3 gives recommendations for clinicians in office practice managing children with both ASD and an elevated BLL.

Hospitalization

Children with ASD and lead poisoning may need to be hospitalized for a number of reasons. If they have a BLL ≥ 70 $\mu\text{g}/\text{dL}$ and/or have evidence of lead encephalopathy, then hospitalization, often triaged to a critical care unit, is the safest course of management. Admittedly, recognizing lead encephalopathy can be difficult in children with ASD who have baseline behavioral problems, though parents are often able to note any changes in their child's mental status. Children with lower BLLs, such as those with BLL 45 to 69 $\mu\text{g}/\text{dL}$, may also require hospitalization for chelation if compliance with oral medication-taking is questionable and/or a lead-safe home environment cannot be assured.

Hospitalization can be a very difficult time for both the patient and their family, especially in a child with ASD. Table 4 lists some recommendations for clinicians to consider when hospitalizing a patient with ASD for inpatient management of severe lead poisoning.

Chelation

Table 5 addresses chelation in children with ASD whose lead poisoning is severe enough to consider use of these medications to lower the body's burden of lead. Details of specific chelants have been reviewed elsewhere.⁴¹ All of the chelants used to treat lead poisoning can have serious adverse effects, such as bone marrow suppression, nephrotoxicity, chemical hepatitis, allergic rashes, and gastrointestinal disturbances. Administration of iron supplementation or foods with milk, zinc, or iron may decrease the absorption of d-penicillamine.⁴² The clinician contemplating use of such medications should review these potential adverse effects with the parents/guardians in obtaining their consent for treatment.

Treating a child with ASD with a parenteral medication like CaNa_2EDTA requires insertion of an intravenous catheter, which in our experience is likely to be pulled out, interfering with the necessary continuous therapy. Nurses are challenged with protecting the IV's (intravenous) integrity in a child with ASD so that therapy is not interrupted.

The oral chelant medications used in medical management of moderate-severe lead poisoning are not "kid friendly." They have sulfur or amines in them causing them to taste bad and smell like rotten eggs. Getting a child with autism to swallow either d-penicillamine or dimercaptosuccinic acid can be a challenge. Disguising the medication by mixing it in a child's favorite food, such as applesauce or peanut butter, is a strategy successfully employed by many parents. However, children with ASD often have restricted diets. By disguising dimercaptosuccinic acid in their food, there is the risk that they will recognize it and potentially reject one of the few foods contributing to their nutrition. Thus, adherence to the twice or 3-times daily dosing schedule can be particularly difficult.

The use of chelants to treat ASD itself in children who do not have documented lead poisoning is discouraged as a scientifically unfounded practice that may produce untoward consequences or even neurotoxic adverse effects.⁴³⁻⁴⁵ Several iatrogenic deaths due to hypocalcaemia have been reported by the mistaken use by alternative practitioners of Na_2EDTA instead of CaNa_2EDTA in the treatment of children with lead poisoning, including children with ASD who had lead poisoning.⁴⁶⁻⁴⁸

Multiple Medications

A child with ASD may be taking a regimen of daily medications, such as anticonvulsants, antipsychotics, or serotonin reuptake inhibitors.⁴⁹ The clinician must be cognizant of concomitant adverse effects if supplemental iron or chelation medications must be added to his or her regimen. There may be new side-effects or little studied drug-drug interactions to consider in the treatment of these patients

Alternative Therapies

Some parents take their children to alternative health care providers for assessment of their ASD. Complementary and alternative therapies proposed in patients with ASD range in safety from generally safe to dangerous and range in efficacy from ineffective to effective to unknown efficacy.⁵⁰ When alternative practitioners find the hair or urine lead elevated, such practitioners may recommend chelation or unconventional, scientifically unsupported, costly, and potentially dangerous detoxification regimens.⁵⁰ These children may have very low BLLs and no evidence of exposure to environmental lead and therefore no need for such management strategies.

Dietary Challenges

Some children with ASD may have nutritional deficiencies, such as iron, calcium, magnesium, or vitamin D. Iron-deficiency anemia is a known comorbidity of childhood lead poisoning.⁵¹ Such deficiencies may result in increased lead absorption through the intestinal wall active transport system for metals. Ensuring adequate dietary or supplemental sources of iron, magnesium, calcium, and vitamin D are likely to help protect the child from lead absorption in the gastrointestinal tract.

Developmental Monitoring and Services

Some children with elevated blood lead levels may have previously undiagnosed ASD or other developmental delays. Indeed, there has been a recommendation that all children with an elevated BLL receive Early Intervention Program services.⁵² Some children with ASD, recognized or unrecognized, may not be getting ABA special educational services for which they are qualified and deserve.

Economics and Social Environment

The lead abatement of a residence often requires days or weeks to accomplish. During the work, for safety, children cannot stay in the house and the family must relocate to a second temporary residence, such as another hazard-free apartment or house, hotel, shelter, or the home of a family member or friend. Such a move interferes with the family's usual routines and transitions the children to new surroundings, which may have noise-level restrictions and other constraints. Children with autism have difficulty tolerating changes in their routine. They often react negatively with transitions and changes in their caretakers, teachers, or living environments. The abatement of lead hazards in a home can be costly to the parents. This adds an economic burden on a family already laboring under multiple stressors. The necessity of close medical monitoring and/or hospitalization requires that the parent miss considerable days of work and may threaten the parent's job security, adding to family stress.

Legal Advocacy

Federal policies and lead regulations in many states protect children under the age of 6 years from lead hazards in their environment, requiring hazard abatement if the child is found to have an elevated lead level and lead-contaminated surfaces are discovered at the time of inspection of their residence. These laws were designed with younger children in mind,

since they are most vulnerable to the deleterious effects of lead and explore their environment through pica and hand-to-mouth behaviors. However, both pica and oral exploratory habits may not extinguish in preschool years in children with ASD and instead persist throughout childhood and into adolescence. Laws regarding residential lead hazards are not adequately protective for children with ASD and persistent pica behaviors living in a contaminated environment. They may not be afforded the same rights to a lead-free environment as younger children who have been exposed to lead.

Conclusions

We have reviewed the prevalence of both childhood lead poisoning and ASD, the neurologic vulnerability of young children to both conditions, the relationship between lead exposure and ASD, and the diagnosis and management of children with both elevated BLL and ASD. Childhood lead poisoning adds a number of considerable burdens to any family's ability to function in everyday life: worrisome long-term health concerns regarding their children, economic considerations in bringing their housing into hazard-free compliance, complex medical protocols and therapies to avert lead's toxic effects, special education needs of the children, transitional housing during residential remediation, insecurity about the safety of secondary homes (eg, uninspected family day care facilities or grandparents' homes), missed time from work and/or school, and parental feelings of guilt, inadequacy, and loss of control. All of these stressors, and more, are magnified in the families of children with ASD and lead poisoning. The astute clinician will recognize where compromises can be made and where adherence to protocol is necessary in the management of these patients. Health care providers must strive to advocate for these families and mitigate the ill effects of lead exposure on their child's development, while maximizing their health as well as their social and educational welfare.

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Table 1.**Recommendations: BLL Testing for Children With ASD.**

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|----------|---|
| 1 | Providers should be aware of local lead-screening guidelines, but also be conscious of the fact that children with ASD may require enhanced or extended screening. |
| 2 | Providers should inquire into pica behaviors for a child with ASD at every well-child visit, especially in a child with comorbid anemia or iron deficiency. |
| 3 | For all preschool children diagnosed with ASD who live in older neighborhoods where lead hazards are likely, testing with BLL should be carried out during well child care at least annually. |
| 4 | Children with ASD who continue to manifest hand-mouth behaviors and ingestion of nonfood items (pica) should be tested with annual BLLs even into later childhood and adolescence. |
| 5 | Lead poisoning should be considered in the differential diagnosis of children with ASD who present to a health care facility with changes in behavior (eg, lethargy, increased irritability, agitation, and increased wakefulness), new gastrointestinal symptoms (eg, new onset anorexia, abdominal pain, and constipation), or new-onset regression in their speech or development. |

Abbreviations: BLL, blood lead level; ASD, autism spectrum disorder.

Table 2.

Key Features: Children With Both Autism Spectrum Disorder and Lead Poisoning.

1	Often affects both preschool and school-aged children, and sometimes adolescents
2	Invariably associated with increased hand-mouth behaviors and/or pica habits
3	Persistent risk of re-exposures over time
4	Increased risk of iron deficiency as a comorbidity due to inadequate dietary sources of iron
5	Poor therapeutic adherence and other behavioral challenges in medical management
6	Need for special educational services
7	Multiple medical, social, educational, housing, and economic stressors on the family

Table 3.

Office Management: Elevated BLL and ASD.

1	Children with both ASD and lead poisoning should be monitored especially closely in their developmental trajectory and placed into any community-based educational services deemed necessary. A number of behavioral interventions are known to be effective in improving outcomes in children with ASD. ⁴⁰
2	Discussion of nutrition in children with lead poisoning and ASD is an important part of the visit. Is the child's diet balanced enough to provide adequate supplies of nutrients? Educating caretakers about good sources of iron, vitamin D, and other nutrients may give them knowledge of alternative foods to try that may be more palatable to the child.
3	Periodic monitoring of blood vitamin D (25-hydroxycholecalciferol) and iron levels can inform dietary counseling and the need for supplemental sources of iron, calcium, and/or vitamin D.
4	Clinicians should be familiar with state and federal regulations related to monitoring for childhood lead exposure as well as remediation and abatement of lead hazards in a child's environment.
5	Clinicians should reach out to medical-legal partnerships on a family's behalf, potentially leveraging the American with Disabilities Act, to advocate for suitable housing accommodations for their patients with ASD and lead poisoning who continue to reside in a home with un-remediated lead hazards.
6	Close coordination with state or local governmental CLPPP is essential. These programs can advise families about grants and loans for which they may be eligible to help defray the economic burden of lead abatement.
7	For clinicians who have resources available in their office, such as social workers or case managers, such personnel can be instrumental in acting as liaisons to community-level resources and helping to coordinate services for families.

Abbreviations: BLL, blood lead level; ASD, autism spectrum disorder; CLPPP, childhood lead poisoning prevention programs.

Table 4.**Hospitalization.**

- 1** Reasons for hospitalization of children with ASD and lead poisoning are much the same as those without ASD. Children exhibiting signs of severe, life-threatening poisoning, such as seizures or encephalopathy, may require triage to a critical care unit. Those with severe poisoning (BLL > 70 µg/dL) will and moderate poisoning (BLL 45–69 µg/dL) may require admission for close neurologic monitoring and administration of chelants, while community-level agencies assess the safety of the home.
- 2** Children with ASD may benefit from nonpharmacologic behavioral interventions while hospitalized for lead poisoning. Behavioral management teams and child life services, if available, can be helpful in providing guidance.
- 3** For children who require continuous intravenous (IV) therapy with CaNa₂EDTA, providing short breaks disconnected from the IV for 1 to 2 hours a day can allow children time to use up pent up energy while still receiving the majority of their medication course.
- 4** Treatment of these children requires a degree of flexibility. Utilizing a 1:1 sitter can help decrease the risk of IV removal.
- 5** Blood draws may require extra helping hands and child life specialists for older children with ASD.
- 6** When urine collection is required for monitoring of nephrotoxic side-effects of chelant medications, cotton balls are a preferred alternative collection method to urinary catheterization in diapered children.

Abbreviations: ASD, autism spectrum disorder; BLL, blood lead level.

Table 5.

Chelation.

- 1 Chelation should not be given to children with ASD who do not have lead poisoning or other heavy metal toxicity.
- 2 Families of children with ASD often seek the advice of alternative medicine practitioners, who may prescribe unconventional, non-evidence-based therapies. It is especially important to maintain a therapeutic alliance and an open line of communication with the family so that the medical provider can serve as a dependable source of reliable medical information.
- 3 Providers who prescribe chelants should be well-versed in their clinical indications and dosing as well as knowledgeable about potential adverse effects.
- 4 In addition to online resources, local pediatricians knowledgeable in lead poisoning, regional poison control centers, or regional Pediatric Environmental Health Specialty Units (PEHSUs) are resources that can provide guidance on chelation therapy.
- 5 Care should be taken to assess for any drug-drug interactions for children being treated for ASD and lead poisoning. Consultation with a pharmacist can be useful before starting these children on new therapies. Alternatively, clinicians can use online institutional formularies or electronic prescribing systems with the capability for checking for drug-drug interactions.
- 6 Clinicians should communicate clear instructions regarding medical regimens to parents.
- 7 A trial of oral medication, under nursing supervision, prior to hospital discharge can help caretakers in medicine-giving to their child, and increasing adherence during outpatient therapy.
- 8 A home visiting nurse may be helpful in working with the family to ensure medication is taken.
- 9 Refrigerated pills (do not freeze them) are less likely to off-gas, decreasing the objectionable pungency of their smell and taste.

Abbreviation: ASD, autism spectrum disorder.