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Microcytic anaemia in neurodivergent children: When iron deficiency masks lead toxicity

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Abstract

Background: Chronic low level lead exposure remains an under recognized cause of microcytic anaemia and neurodevelopmental impairment in children. Early diagnosis is challenging when symptoms overlap with Iron Deficiency Anaemia (IDA) or neurodevelopmental disorders such as Autism Spectrum Disorder (ASD).

Case presentation: We report two Belgian children with refractory IDA and neurodevelopmental symptoms, ultimately linked to renewed lead exposure from deteriorating household paint. Case 1, a seven year old girl with a history of pica and prior lead intoxication, re presented after being lost to follow up with persistent microcytic anaemia and elevated Blood Lead Level (BLL). Case 2, a four year old girl with ASD and severe pica, presented with profound anaemia and a moderately elevated BLL. In both cases, chelation therapy was not indicated, as BLL remained below 45 µg/dL. Management focused on environmental source remediation and iron supplementation.

Conclusions: Persistent or recurrent IDA, especially in children with pica or ASD, should lead to systematic BLL testing even when values are anticipated to be “low”. Vigilant follow up after an initial episode is essential to prevent re exposure and progressive neurotoxicity.

Keywords: Lead poisoning; Anaemia; Microcytic; Autism spectrum disorder; Pica; Environmental health; Child neurology.

Abbreviations: IDA: Iron Deficiency Anaemia; ASD: Autism-Spectrum Disorder; BLL: Blood Lead Level; MCV: Mean Corpuscular Volume.

Introduction

Lead remains a pervasive environmental toxicant and an underrecognized contributor to pediatric morbidity, especially due to its insidious effects on neurodevelopment and hematologic function [1,3]. Children are especially vulnerable because of increased gastrointestinal absorption and the heightened

plasticity of the developing brain [2,3]. Clinical presentation is often indirect, typically through persistent microcytic anaemia refractory to iron supplementation or subtle behavioral and developmental changes [4,7]. These signs should prompt investigation for environmental lead exposure, especially in children with pica or neurodevelopmental disorders such as ASD.

These cases illustrate key diagnostic challenges and highlight the importance of repeated Blood Lead Level (BLL) screening in at-risk groups.

Case presentations

Case 1

A 7-year-old girl of Moroccan origin, with a past history of IDA and lead poisoning at age 4, initially attributed to pica, had partially improved on oral iron but never normalized. No environmental investigation was conducted, and she was lost to follow-up. At age 7, she re-presented with persistent fatigue, food selectivity, and behavioral deterioration. Examination was unremarkable. Laboratory testing revealed microcytic anaemia (hemoglobin 10.5 g/dL, mean corpuscular volume 63.9 fL, ferritin 6 µg/L) and elevated BLL at 13.85 µg/dL, confirming re-exposure. Alternatives causes of anaemia were excluded, and an abdominal X-ray was performed to rule out ingested radiopaque foreign bodies as a potential source of lead. Neurological reassessment revealed language delay and behavioral features suggestive of ASD. Chronic lead exposure was considered a potential aggravating factor in the patient’s neurodevelopmental condition. As BLL remained below the threshold for chelation (<45 µg/dL), treatment consisted of oral iron supplementation (6 mg/kg/day) and environmental intervention. An inspection identified flaking lead-based paint on an interior doorframe as the probable source. The father’s occupation in construction and renovation was considered a possible contributor to secondary household contamination. Following removal of the paint, BLL decreased to 9.38 µg/dL and hemoglobin normalized within three months. Family screening revealed elevated BLLs in all three siblings: the 14-year-old (6.18 µg/dL, hemoglobin 11.9 g/dL), the 11-year-old (4.71 µg/dL, hemoglobin 12.4 g/dL), and the 8-month-old (2.89 µg/dL, hemoglobin 11.0 g/dL). Both parents tested negative for lead and anaemia. According to local laboratory thresholds, only the infant exceeded the toxic limit (≥2.5 µg/dL for children <7 years); the older children fell below their respective cut-offs (≥5 µg/dL for ages 7-11; ≥10 µg/dL for ≥12 years). However, a follow-up test in the infant showed a rising BLL (3.76 µg/dL, hemoglobin 12.4 g/dL). Based on updated CDC reference values (≥3.5 µg/dL for all children), all siblings qualified as lead-exposed and are currently undergoing neurological assessment and long-term monitoring.

Table 1: Laboratory findings - Case 1 (7-year-old girl).

Parameter	4 years ago	3 years ago	Before lead removal	3 months after removal
Hemoglobin (g/dl)	9.8	12.5	10.5	13
MCV (fL)	60	68	63.9	73.2
Ferritin (µg/L)	10	12	6	21
Blood lead level (µg/dL)	9.5	5.5	13.85	9.38

Case 2

A 4-year-old girl of Ukrainian origin, with a known diagnosis of ASD, was referred for persistent microcytic anaemia unresponsive to appropriately conducted oral iron supplementation, as confirmed by caregivers. She was under regular pediatric neurology follow-up for developmental concerns. Targeted clinical

reassessment identified pica behavior involving the ingestion of wall material, which had not been previously reported and was recognized only after the unexpected association of refractory anaemia and behavioral changes. Physical examination was unremarkable, with no signs of abdominal pain, encephalopathy, or gingival lead lines. Laboratory workup revealed severe microcytic anaemia (hemoglobin 6.4 g/dL, mean corpuscular volume 54.5 fL, ferritin 2 µg/L) and an elevated BLL of 5.25 µg/dL. Additional investigations ruled out other causes of microcytic anaemia: hemoglobin electrophoresis was normal, and inflammatory and celiac screening tests were negative. Given the moderate BLL, chelation therapy was not indicated. Management focused on eliminating the environmental source and correcting iron deficiency through intravenous iron supplementation (15 mg/kg/dose). An environmental assessment identified deteriorating lead-based wall paint as the probable source of exposure. As in Case 1, the child’s father worked in the renovation industry, raising concern for potential secondary lead contamination at home. Four months after intervention, hemoglobin levels had normalized, and follow-up BLL showed a significant decrease, confirming treatment efficacy and source elimination. Family screening, including a 14-year-old sibling, revealed no lead exposure or anaemia.

Table 2: Laboratory findings - Case 2 (4-year-old girl).

Parameter	Before lead removal	4 months after removal
Hemoglobin (g/dl)	6.4	13
MCV (fL)	54.5	75.2
Ferritin (µg/L)	2	8
Blood lead level (µg/dL)	5.25	4.83

Discussion

The clinical complexity of pediatric lead poisoning is well illustrated by the two cases presented. In the first case, persistent lead exposure likely contributed to the progressive worsening of neurological symptoms, including developmental delay and language impairment. This underscores the critical need for rigorous and continuous follow-up after an initial diagnosis to monitor for re-exposure and prevent cumulative neurotoxicity. Unfortunately, in this case, insufficient surveillance may have led to a deterioration in the patient’s clinical status over time.

The second case was identified thanks to insights gained from the first patient. This child, diagnosed with ASD and refractory anaemia, was tested for lead poisoning after neurological symptoms emerged and targeted questioning revealed pica behavior. This case highlights the value of heightened clinical suspicion and proactive screening for lead exposure, particularly in children with neurodevelopmental disorders, where behavioral and environmental risks intersect [4,6]. These observations reinforce the need to consider environmental lead exposure in any atypical anemia or unexplained developmental regression [1,8]. Lead poisoning remains a significant yet often underestimated cause of pediatric morbidity, primarily due to its profound effects on neurodevelopment and hematologic function. Environmental exposure typically occurs through deteriorating lead-based paint, contaminated dust or soil, home renovations, as well as other sources such as contaminated water, traditional medicines, or parental occupational exposure

[5,9]. Behavioral factors including pica and frequent hand-to-mouth activity substantially increase ingestion risk, especially in young children and those with neurodevelopmental disorders [4,7]. Diagnosing lead poisoning remains challenging due to its hematologic presentation closely mimicking IDA, characterized by microcytic, hypochromic anaemia and sometimes basophilic stippling [1]. However, basophilic stippling, although classic, lacks both sensitivity and specificity; consequently, blood lead level measurement is indispensable to confirm diagnosis and guide appropriate management.

Case 1 illustrates how relapse may go unnoticed without routine re-screening after apparent clinical recovery. Furthermore, emerging evidence shows that blood lead levels below the historically accepted threshold of 10 µg/dL can still cause adverse neurodevelopmental effects [5,10]. In 2012, the CDC's former Advisory Committee on Childhood Lead Poisoning Prevention recommended lowering the reference BLL to 5 µg/dL. This value was further revised in 2021, when the CDC updated the reference value to 3.5 µg/dL, reflecting the growing recognition that no blood lead level is truly safe in children [11]. Iron deficiency has been consistently associated with increased lead absorption, likely due to overlapping intestinal uptake mechanisms. As a result, low iron status not only contributes to anaemia but also enhances the body's susceptibility to lead toxicity [12,13]. Correcting iron deficiency is therefore crucial, not only to restore hematologic parameters but also to help reduce ongoing lead absorption. Our cases illustrate this interaction: in particular, intravenous iron therapy in Case 2 led to a rapid hematologic response and likely contributed to the subsequent decline in blood lead levels. Neurotoxicity remains the most serious consequence of lead exposure in children. Even BLLs once considered "low" (<10 µg/dL) are now recognized to impair cognitive function and behavior, with well-documented associations to reduced IQ, attention deficits, language delays, and emotional dysregulation [2,10]. Early childhood, particularly under five years of age, is a critical period of rapid brain development and synaptic pruning, during which the brain is especially vulnerable to environmental toxicants. Lead exerts its neurotoxic effects by interfering with calcium-mediated signaling and disrupting neurotransmission across cholinergic, dopaminergic, glutamatergic, and GABAergic pathways [14]. These alterations may manifest as distractibility, hyperactivity, irritability, learning difficulties, and behavioral regression [2,3].

Although blood lead levels may decrease following intervention, the lead that has already accumulated in brain tissue continues to exert harmful neurotoxic effects [3,15]. Consequently, detection of elevated blood lead occurs too late to fully prevent neurological damage, even when chelation therapy is administered. Therefore, primary prevention of avoiding any lead exposure in children or ensuring rapid detection is essential to protect the developing brain. Children with neurodevelopmental disorders, especially ASD, appear to be doubly vulnerable. Repetitive pica behaviors increase the risk of lead exposure, while underlying neurodevelopmental impairments may amplify the toxic effects of even modest lead burdens [5]. Although lead is not causally linked to ASD, it can exacerbate pre-existing deficits in language, memory, and stress regulation. Moreover, rare cases of misdiagnosis can occur with high BLL, where lead-induced cognitive and behavioral impairments mimic core features of ASD [6,7]. Our clinical cases illustrate this complex interplay: both children presented with persistent behavioral symptoms despite intervention, and lead exposure was only identified upon further evaluation. These cases emphasize

the need for routine blood lead screening in children with neurodevelopmental disorders, particularly when anaemia, pica, or behavioral regression are present.

Management primarily involves eliminating sources of lead exposure, mitigating behavioral risks, and correcting nutritional deficiencies. Chelation therapy is typically reserved for severe cases (symptomatic children or those with BLL exceeding 45 µg/dL) [1,15], as its benefits on neurocognitive outcomes at lower levels remain limited and because of the risk of adverse effects such as fever, rash, renal dysfunction, and marrow suppression [5]. Four chelating agents currently recognized for lead poisoning treatment include dimercaprol, calcium disodium edetate, dimercaptosuccinic acid (DMSA, e.g., succimer), and D-penicillamine [5,8], with DMSA being the preferred option in children [8]. These agents bind circulating lead ions and promote their urinary excretion. However, they have minimal effect on lead already stored in deep compartments such as bone and brain, where it can persist for years (with a half-life of approximately two years) and continue to cause neurotoxicity. This highlights the critical importance of early diagnosis and primary prevention [3].

Conclusion

These cases highlight the critical importance of testing BLL in children with microcytic anaemia, especially when the anaemia is refractory to iron supplementation. The need is even more pressing in children presenting with neurodevelopmental symptoms or diagnosed with ASD, where lead exposure may be masked by overlapping clinical features. Targeted lead screening in these high-risk groups enables earlier diagnosis, prevents ongoing exposure, and reduces the risk of irreversible cognitive and behavioral sequelae. Therefore, routine inclusion of lead testing in the diagnostic workup of refractory IDA should become a standard practice in at-risk populations.

Finally, these cases emphasize the importance of maintaining pediatrician vigilance and ensuring that new generations of physicians are trained to recognize lead toxicity, as lead, despite its declining use, remains a significant and often underestimated threat.

Declarations

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Ethics approval and consent to participate: This case report is in accordance with the journal's ethics and integrity policies.

Competing interests: The authors declare that they have no competing interests.

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