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Original Article

Evaluation of lead levels in children with chronic constipation

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ABSTRACT

Objectives. This study aimed to assess blood and hair lead levels (BLL and HLL) in children with chronic constipation and compare them to healthy children; and investigated lead exposure's role in the etiology of constipation. It also explored the correlation between BLL and HLL.

Study Design. The study included 84 constipated children aged 3-18 years as the case group and an equal number of constipation-free children as controls. Organic diseases were ruled out through history-taking, physical exams and laboratory tests. Blood and hair samples were collected and analyzed for lead levels using standardized methods.

Results. The constipated children group had significantly higher BLL (3.66 µg/dL) compared to the control group (1.61 µg/dL) with no significant HLL difference. Additionally, 48.8% of constipated children exceeded the reference value of 3.5 µg/dL, in contrast to 4.8% of the control group. BLL was unaffected by gender and age, while HLL were higher in girls and low ages. No significant correlation existed between BLL and HLL. The age of the housing showed a positive correlation with higher BLL and HLL. Lead exposure sources like drinking water, home renovation history, parental smoking, or nearby industrial facilities showed no significant relationships with lead levels.

Conclusions. Understanding the constipation-lead exposure link is crucial for prevention and intervention. HLL may vary with gender and age due to external lead particles, which is why BLL continues to be a more reliable measure. Healthcare providers should remember to investigate lead exposure risk factors in constipation patients and test BLL when necessary.

Key words: constipation, lead, blood lead level, hair lead level.

Constipation is defined as infrequent or difficult bowel movements, diagnosed according to the ROME IV criteria. Constipation accounts for 3% of general pediatric clinic admissions and 25% of pediatric gastroenterology and hepatology clinic admissions.[1,2] Only 5% of constipated children have an organic cause, while no organic cause can be found in 95% of cases.[3] Heavy metal exposure, particularly lead, has emerged as a significant factor among the many potential organic contributors to constipation.[4-6] Lead exposure was primarily attributed to the use of leaded gasoline from the 1920s until the present. Leaded gasoline is no longer available worldwide as of 2021 due to the depletion of the last leaded gasoline refinery in Algeria. Thus the world has bid farewell to this source of lead contamination.[7,8] Other routes of exposure

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include water distribution systems, dietary sources, medications, toys, and jewelry.[9]

The adverse effects of lead extend across various body systems, impacting the nervous system, gastrointestinal system, as well as the cardiovascular, genitourinary, and hematopoietic systems. In the gastrointestinal system, abdominal pain, cramps, constipation, nausea, vomiting, bloating, and weight loss may occur.[10,11] It is hypothesized that lead causes constipation via direct inhibitory effects on the neural plexus of the intestine and also on smooth muscle contractions.[12] Additionally, metabolic alterations, such as the accumulation of δ-aminolevulinic acid (a porphyrin precursor), resulting from lead-induced porphyrinopathy, also diminish intestinal motility. Moreover, lead alters the stimulation of the cell membrane through changes in the activity of cell membrane channels, which is also implicated in the occurrence of constipation.[13]

Measuring lead levels in whole blood is the most used and considered most reliable method for demonstrating, monitoring, determining the treatment method when necessary, taking protective measures, and performing screening programs for lead exposure. On May 14, 2021, the Lead Exposure Prevention and Advisory Committee (LEPAC) updated the reference value for children's blood lead levels (BLL) from 5 μg/dL to 3.5 μg/dL.[14]

Although measuring lead levels in blood is the gold standard test, it is not possible to distinguish between long-term exposure to lead and short-term exposure to high levels of lead by measuring BLL. Moreover, the lead level in the blood represents only a small fraction of the total lead burden in the body and may not be a favorable reflection of the total lead load. Therefore, there is a need to measure lead levels from different samples, such as hair in addition to blood.[15-17]

This study aimed to assess BLL and hair lead levels (HLL) in children with chronic constipation and compare them to healthy children and investigated lead exposure's role in constipation etiology. It also explored the correlation between BLL and HLL.

Materials and Methods

The study included 168 participants divided into two groups, each with 84 children. The case group comprised children aged 3 to 18 who visited our clinic with complaints of constipation between February 2022 and July 2023. The study was conducted in Istanbul a densely populated urban area. The control group consisted of 84 children matched for age and gender, who were scheduled for blood tests in the outpatient clinic for various reasons, had no complaints of constipation, and had no chronic illnesses. In this study, constipation was defined as infrequent or difficult defecation lasting for two months or longer. A rigorous selection process was implemented for both groups to ensure the accuracy of the study. This process included comprehensive medical history evaluations, physical examinations, and laboratory tests. We excluded any organic diseases as the potential cause of constipation in all participants. In the course of our investigation, children who were fed solid and low-fiber foods and had inadequate fluid intake were excluded from the study. Accordingly, both groups underwent a standardization process in terms of dietary habits. Written informed consent was obtained from the parents of all participating children. Exclusion criteria included refusal to participate in the study or provide blood and hair samples. Demographic information forms were completed by the parents, which included details such as the age of their homes, history of home renovations, method of obtaining drinking water, presence of nearby factories, and family history of smoking.

The study was approved by the local ethics committee on January 13, 2022, under decision number E-46716. Additionally, it was supported by the Bezmialem Vakıf University Scientific Research Projects Coordination Unit under project number 20220201, as decided on

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Blood sample collection and blood lead level measurement

After obtaining written informed consent from their parents, blood samples were collected from the participants. To maintain sterility, the relevant skin area was cleaned with ethyl alcohol before blood collection. The blood was collected using single-use vacuum needle tips into EDTA-containing tubes, ensuring a minimum volume of 2 mL. The tubes were then stored in a refrigerator at +4°C until the day of testing.

Standard solutions were prepared by diluting the lead stock standard solution of 1000 µg/mL in blood samples. These solutions were appropriately vortexed, and 10 µL of each solution were injected into the graphite furnace using an automatic sampler. The electrothermal graphite furnace atomic absorption spectrophotometry method was employed to measure BLLs, creating an automatic calibration curve. The results were reported in µg/dL.

Hair sample collection and hair lead level measurement

Hair samples were collected from the upper occipital region of the scalp based on a minimum weight criterion of 0.3 grams. The samples were obtained from the hair root using scissors and stored in plastic bags in a dry environment until the day of testing.

Lead levels in the hair samples were measured using ICP-MS (Inductively Coupled Plasma – Mass Spectrometer) Thermo/X series 2 equipment. The analytical method for detecting heavy metals in these samples followed the chemical analysis clinical study guide of the Hewlett Packard Company Group. A 0.25-gram hair sample was dissolved in 5 mL of HNO3 using a microwave (Cem MARS 5). The dissolution process was conducted under conditions of 600 psi pressure and 200°C. After cooling, the sample was diluted with distilled water to a final volume of 25 mL, transferred to polyethylene tubes, and placed in the ICP automatic sampler for measurements.

Statistical analysis

The study included 84 patients in each group, based on previous research with a 95% confidence level and 80% power, as recommended by the literature. The mean difference was 1.5 units, with a standard deviation of 3.5 units. The data were analyzed using IBM SPSS Statistics 22.0 software. Continuous variables were assessed using the t-test, while the chi-square test was employed to analyze categorical variables between groups. The study presented descriptive statistics, including mean ± standard deviation, frequency, and percentage values. The level of statistical significance was determined by a p-value of less than 0.05. For the correlation assessment between BLL, HLL, children's age, and building age, Spearman's rho was utilized. This nonparametric test is appropriate for evaluating the strength and direction of the associations between ranked variables. Correlation coefficients (r_s) were calculated to determine the relationships, with significance levels set at $p < 0.05$ for moderate correlations and $p < 0.01$ for strong correlations.

Results

The study involved 168 children aged 3 to 18 years. The case group was comprised of 46 boys (54.8%) and 38 girls (45.2%), while the control group consisted of 45 boys (53.6%) and 39 girls (46.4%). The mean age of the case group was 7.21 years, and the mean age of the control group was 7.23 years. The study revealed no statistically significant differences between the case and control groups with regard to the age of the building, history of home renovation, type of drinking water and children whose parents smoked. Consequently, the case and control groups were statistically matched in terms of age, gender and other characteristics that may affect lead levels (Table I).

Table I. Characteristics of children with constipation and controls.

Parameter		Case group (n=84)	Control group (n=84)	p*
Sex	Male, n (%)	46 (54.8%)	45 (53.6%)	0.877
	Female, n (%)	38 (45.2%)	39 (46.4%)	
Age, yr	Mean±SD	7.21±4.15	7.23±4.20	0.971
	Median (Q1-Q3)	6 (4-10)	6 (4-9)	
Building age, yr	Mean±SD	20.44±11.55	17.79±12.07	0.087
	Median (Q1-Q3)	20 (10-30)	15 (9.2-25)	
House renovation, n (%)	Yes	28 (33.3%)	23(27.4%)	0.401
	No	56 (66.7%)	61(72.6%)	
Drinking water, n (%)	Tap water	6 (7.1%)	6 (7.1%)	0.625
	Tap water with filter	47 (56%)	41 (48.8%)	
	Bottled water	31(36.9%)	37 (54.4%)	
Smoking parent, n (%)	Yes	40 (47.6%)	43 (51.2%)	0.643
	No	44 (52.4%)	41(48.8%)	

In this study, we examined the lead levels of children with and without constipation. The highest BLL recorded was 9.1 µg/dL, and the highest HLL was 9.83 µg/g. The mean BLL was 2.63 µg/dL, and the mean HLL was 1.07 µg/g in the 168 children (Table II).

Children with constipation in the case group had an average BLL of 3.66 µg/dL, which was significantly higher than the control group's average of 1.61 µg/dL (p<0.001, Table II).

The mean HLL of children in the case group with constipation was 1.26 µg/g, while the mean HLL of children in the control group was 0.88 µg/g. However, there was no statistically significant difference in HLL between the two groups (p=0.801, Table II).

The BLL of 48.8% of children with constipation exceeded the reference value of 3.5 µg/dL, whereas only 4.8% of children in the control group exceeded this reference value. This indicates that the likelihood of BLL being above the reference value in children with constipation was ten times higher than in the control group.

The mean BLL for boys was 2.54 µg/dL, while for girls it was 2.74 µg/dL. There was no statistically significant difference in BLL between the two groups (p=0.508, Table III). When comparing the HLL of male and female children in our study, we found that boys had a mean HLL of 0.88 µg/g, while girls had a significantly higher mean HLL of 2.74 µg/g (p<0.001, Table III).

There was no significant relationship between BLL and the ages of children (p=0.464). However, a significant negative correlation was found between HLL and the ages of children, indicating a low-degree negative relationship (p<0.001, r_s=0.3).

When statistically analyzing the relationship between the levels of lead in the blood and hair, no significant correlation was found between the two groups (p=0.414, r_s=0.063).

Table II. Blood and hair lead levels in constipation and control groups.

Lead levels	Group	Min-Max	Mean±SD	Median (Q1-Q3)	P*
Blood (µg/dL)	Case	1 – 9.1	3.66±1.90	3.4 (2.2-4.97)	<0.001
	Control	0-5	1.61±1.13	1.45 (1-2.27)	
Hair (µg/g)	Case	0.02 – 9.83	1.26±1.67	0.72 (0.3-1.61)	0.801
	Control	0.04 – 2.81	0.88 ± 0.58	0.8 (0.33-1.38)	

Analyzing the correlation between the age of the building and lead levels in children, we discovered a statistically significant positive correlation between the age of the building and both blood ($p<0.001$; $r_s=0.28$) and hair ($p=0.02$, $r_s=0.179$) lead levels. We found no statistically significant difference between individuals with and without a history of home renovation in terms of BLL (p=0.372) and HLL (p=0.628) The study found no statistically significant relationship between the type of drinking water and blood and HLL (p=0.683 for BLL; p=0.656 for HLL) We found no statistically significant difference in lead levels between children whose parents smoked and those whose did not (p=0.354 for BLL; p=0.655 for HLL, Table III).

When examining the effect of factories or industrial establishments in close proximity to homes on their lead levels, we found that the mean BLL was 2.63 μg/dL and the mean HLL was 1.10 μg/g for those without such establishments nearby. However, individuals living near factories had a significantly higher mean BLL of 2.66 μg/dL and mean HLL of 0.89 μg/g. Our study found no statistically significant difference in lead levels between the two groups: those with and without a factory near their homes (p=0.792 for BLL; p=0.522 for hair lead, Table III).

Discussion

Lead is the most implicated heavy metal in constipation, and lead exposure is one of the preventable causes of constipation. Therefore, in our study, BLL and HLL of constipated and healthy children were evaluated to elucidate the etiology of chronic constipation. On May 14, 2021, the CDC's LEPAC updated the children's blood lead reference value from 5 μg/dL to 3.5 μg/dL (0.17 μmol/L). The updated value reflects the latest scientific evidence on the harmful effects of lead exposure on children, but the CDC emphasizes that there is no safe BLL and that even very low lead levels can cause neurodevelopmental effects. In our study, the mean BLL in the constipation group was above the reference value of 3.5 μg/dL, while the mean BLL in the control group was below this reference value. When the BLLs of

Table III. A comparison of blood and hair lead levels according to the distinctive characteristics of the patients.

	Parameters		n	Mean±SD	Median (Q1-Q3)	p*
Blood lead levels (μg/dL)	Sex	Male	91	2.54±1.76	2.1 (1.2-3.3)	0.508
		Female	77	2.74±1.99	2.5 (1.2-4.1)	
	House renovation	No	117	2.52±1.76	2.1 (1.3-3.45)	0.372
		Yes	51	2.89±2.08	2.5 (1.2-3.9)	
	Drinking water	Tap water	12	2.77±1.26	2.5 (2.02-3.5)	0.683
		Tap water with filter	88	2.72±2.07	2.35 (1.1-3.75)	
		Bottled water	68	2.50±1.69	2.1 (1.2-3.45)	
	Smoking parent	No	85	2.79±1.89	2.1 (1.3-3.85)	0.354
		Yes	83	2.47±1.84	2.3 (1.1-3.5)	
Hair lead levels (μg/g)	Sex	Male	91	0.88±1.21	0.47 (0.24-1.29)	<0.001
		Female	77	1.29±1.28	1.14 (0.57-1.54)	
	House renovation	No	117	1.08±1.19	0.81 (0.33-1.44)	0.628
		Yes	51	1.03±1.42	0.64 (0.3-1.44)	
	Drinking water	Tap water	12	1.15±1.21	0.77 (0.28-1.7)	0.656
		Tap water with filter	88	1.10±1.15	0.63 (0.28-1.43)	
		Bottled water	68	1.02±0.78	0.87 (0.35-1.42)	
	Smoking parent	No	85	0.95±0.9	0.81 (0.31-1.44)	0.655
		Yes	83	1.19±1.54	0.71 (0.32-1.44)	

the two groups were compared, it was found that the BLL of the group with constipation was statistically significantly higher than that of the group without constipation. In the constipation group, 48.8% of children had BLL above the reference value, while only 4.8% of children in the control group had elevated levels. These results suggest that children with constipation are at a ten times higher risk of lead exposure than those without constipation. In February 2023, Zamani et al. conducted a study on 237 children with chronic constipation. The study found that 20.67% of patients with constipation had BLL ≥ 5 μg/dL and the mean BLL in children with chronic constipation was 3.51 μg/dL.[12] These results indicate that BLL in children with chronic constipation are above the reference value, which is consistent with our study. This emphasizes the importance of lead as a potential cause of constipation and highlights the necessity of investigating lead exposure in its etiology.

According to the CDC's LEPAC, it is recommended that children be screened for lead levels twice, at 12 and 24 months of age. If a child is not screened at 24 months of age, it is recommended that they be screened at least once before they reach 72 months of age. For those who cannot be screened, it is important and recommended to identify high risk groups and check BLLs.[12] As there is currently no screening program in our country, the children in the study had not been previously screened for lead. Our study analyzed children aged 3-18 years, which is the upper limit of the age range covered by the screening program recommended by the CDC. The findings of our study are important for contributing to research on the effectiveness of screening programs by comparing them with other countries that implement screening programs.

Our study shows that the average BLL in our country are higher than in the United States.[9] This can be attributed to the continued use of lead-based paints and the absence of a screening program.

Research on lead in our country has been limited in scope, primarily involving small numbers of individuals, and remaining regional. However, studies conducted after the removal of leaded gasoline have shown a significant decrease in BLLs in children, especially in areas with heavy traffic. For example, a study conducted in İstanbul in 2013 found that the average BLL in children decreased from 8.4 μg/dl in 2000 to 1.84 μg/dL. Another study from our team, found that the average BLL of healthy children in İstanbul was 1.61 μg/dL, indicating a decrease since 2013.[18,19]

The available studies on lead levels in children with constipation are limited. Sevinc et al. found that BLLs were 5.12 μg/dL in the functional gastrointestinal disease group, 12.29 μg/dL in the functional constipation group, and 1.77 μg/dL in the control group.[20] Consistent with our study, it was observed that BLLs were significantly higher in the constipation group than in the control group. However, Sevinc et al.'s study on children in Karabük found higher lead levels in both the control group and the constipation group compared to our study. This difference may be explained by the higher density of industrial establishments and factories in Karabük compared to İstanbul, but more comprehensive studies are needed.

HLL can be measured as an alternative to BLL due to the ease of collection and storage, low cost and transport to the laboratory. In this study, the mean HLL of children in the control group was 0.88 μg/g, while the mean HLL of children with constipation was 1.26 μg/g. Adams et al. conducted a study in 2006 comparing the mean HLL of healthy children and children with autism spectrum disorder.[21] The results showed that the mean HLL of healthy children was 0.81 μg/g, while that of children with autism spectrum disorder was 0.62 μg/g. These results are similar to the HLL found in healthy children in our study. Although there have been many studies on HLL in children, a reference level for HLL in healthy children has not yet been established.[22] Our study could serve as a resource for future research to establish reference values for HLL.

This is the first study to evaluate HLL and BLL together in children with and without constipation. The results indicate that there is no statistically significant difference in HLL between constipated and non-constipated children. This lack of difference may be due to the fact that it takes years for lead to accumulate in the hair or that external lead particles adhere to it, affecting the measured lead levels.

No significant correlation was found ($p=0.41$, $r_s=0.06$) when analyzing the relationship between blood and HLL in our study. According to the current literature review, Iaquinta et al. also found no correlation between hair and blood in their study conducted in January 2024.[23] The Toxicological Profile for Lead guideline of ATSDR, published in August 2020, states that HLL measurement is a relatively poor predictor, which is consistent with our findings.[24] The lack of correlation between lead particles and hair can be attributed to the adherence of exogenous lead particles to the hair. These particles adhere to the hair via dust, and there is currently no gold standard washing method to completely remove them. The study by Morton et al. demonstrated that the hair washing method recommended by the International Atomic Energy Agency is insufficient to completely remove exogenous lead from hair.[25] According to a study by Renshaw et al. exogenous lead particles tend to accumulate more in the distal part of the hair, resulting in a higher concentration of lead in the distal part compared to the proximal part.[26] Several studies have shown that various factors, such as age, gender, hair color, smoking, and ecological factors (geographical, racial/ethnic), can influence lead levels in hair. Schuhmacher et al. found that girls had higher HLL than boys, and that HLL decreased with age.[27] Finally, in 2020, Vigeh et al. conducted a study that found a negative correlation between lead levels in the hair of Iranian children and their weight.[28] The study also found that HLLs were higher in girls than boys. In our study, in agreement with previous studies, HLLs were higher in girls than in boys, but no significant difference in BLLs was observed between the sexes. This may be explained by the fact that exogenous lead particles adhere more to the hair of girls because their hair is longer. In this study, we found that BLLs did not vary with age, but we observed a negative correlation between age and HLLs. This tendency for HLL to decrease with age has been observed in numerous studies, including our own.[27,29] This may be attributed to exogenous particles adhering to the hair. It is possible that young children have more contact with lead dust on the ground, leading to increased exposure to exogenous lead particles and higher lead levels. Our study concludes that hair is not a reliable material to measure endogenous lead exposure due to the influence of exogenous lead particles on lead levels. However, further research is needed to investigate the correlation between lead levels in hair and exogenous lead particles.

In our study, we observed that as the age of the homes in which children lived increased, so did the lead levels. This data supports the information provided by the CDC that children living in older homes are at higher risk of lead exposure.[8] This may be due to the greater use of lead-based paint in older homes and the increased exposure of children to paint particles.

The CDC also lists drinking water used in homes as a source of lead exposure and lead pipes that deliver water to homes are blamed.[8] In our study, children were categorized according to the type of drinking water they used, but no statistically significant association was found between the type of drinking water and BLL and HLL. This finding may be due to the reduced use of lead pipes in plumbing systems in our country.

Smoking and exposure to cigarette smoke have been linked to lead exposure.[8] Wolfsperger et al. found that HLL were higher in young healthy adult smokers than in nonsmokers.[30] In our study, we compared the BLL and HLL of children with parents who smoke to those with non-smoking parents and found no significant difference. The absence of a correlation may be due to parents refraining from smoking around their children and reducing their direct exposure to cigarette smoke. However, further extensive research is required to investigate this matter.

Finally, understanding the constipation-lead exposure link is crucial for prevention and intervention. Healthcare providers should remember to investigate lead exposure risk factors in constipation patients and test BLL when necessary. Few studies have looked at BLL and HLL together in children, and none have looked at their association with constipation. This study is the first of its kind, which makes it important. However, it is limited by the relatively small number of children included, so more comprehensive studies are needed to better understand the role of lead levels in the etiology of chronic constipation and to assess the impact of different methods of measurement other than blood, such as hair.

Ethical approval

This study was approved by the Bezmialem Vakıf University Clinical Research Ethics Committee on January 13, 2022 (Decision number E-46716).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: AZG, GD; data collection: AZG, GD; analysis and interpretation of results: AZG, GD, AT; draft manuscript preparation: AZG. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Aziz I, Whitehead WE, Palsson OS, Törnblom H, Simrén M. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol 2020; 14: 39-46. https://doi.org/10.1080/17474124.2020.1708718
2. Benninga M, Candy DC, Catto-Smith AG, et al. The Paris Consensus on Childhood Constipation Terminology (PACCT) Group. J Pediatr Gastroenterol Nutr 2005; 40: 273-275. https://doi.org/10.1097/01.mpg.0000158071.24327.88
3. Inan M, Aydiner CY, Tokuc B, et al. Factors associated with childhood constipation. J Paediatr Child Health 2007; 43: 700-706. https://doi.org/10.1111/j.1440-1754.2007.01165.x
4. Tabbers MM, Boluyt N, Berger MY, Benninga MA. Clinical practice: diagnosis and treatment of functional constipation. Eur J Pediatr 2011; 170: 955-963. https://doi.org/10.1007/s00431-011-1515-5
5. Nurko S, Zimmerman LA. Evaluation and treatment of constipation in children and adolescents. Am Fam Physician 2014; 90: 82-90.
6. Bushnell PJ, Jaeger RJ. Hazards to health from environmental lead exposure: a review of recent literature. Vet Hum Toxicol 1986; 28: 255-261.
7. World Health Organization Regional Office for Europe European Environment and Health Information System (ENHIS). Exposure of children to chemical hazards in food. 2007. Available at: https://iris.who.int/bitstream/handle/10665/370951/WHO-EURO-2007-6412-46178-66793-eng.pdf?sequence=1 (Accessed on January 1, 2024).
8. National Geographic. Finally, the end of leaded gas. 2021. Available at: https://www.nationalgeographic.com/environment/article/finally-the-end-of-leaded-gas (Accessed on January 1, 2024).
9. Centers for Disease Control and Prevention (CDC). Childhood lead poisoning prevention. Sources of lead exposure. 2023. Available at: https://www.cdc.gov/lead-prevention/prevention/index.html (Accessed on January 1, 2024).
10. Surkan PJ, Zhang A, Trachtenberg F, Daniel DB, McKinlay S, Bellinger DC. Neuropsychological function in children with blood lead levels <10 microg/dL. Neurotoxicology 2007; 28: 1170-1177. https://doi.org/10.1016/j.neuro.2007.07.007

11. Dietrich KN, Krafft KM, Bornschein RL, et al. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 1987; 80: 721-730. https://doi.org/10.1542/peds.80.5.721

12. Zamani N, Hosseini A, Farnaghi F, et al. Blood lead level evaluation in children presenting with chronic constipation in Tehran-Iran: a cross-sectional study. Sci Rep 2023; 13: 2301. https://doi.org/10.1038/s41598-023-29487-y

13. Shabani M, Hadeiy SK, Parhizgar P, et al. Lead poisoning; a neglected potential diagnosis in abdominal pain [published correction appears in BMC Gastroenterol 2021; 21: 411.]. BMC Gastroenterol 2020; 20: 134. https://doi.org/10.1186/s12876-020-01284-1

14. Ruckart PZ, Jones RL, Courtney JG, et al. Update of the blood lead reference value - United States, 2021. MMWR Morb Mortal Wkly Rep 2021; 70: 1509-1512. https://doi.org/10.15585/mmwr.mm7043a4

15. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, Parsons PJ. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect 2005; 113: 1669-1674. https://doi.org/10.1289/ehp.7917

16. Rabinowitz M, Leviton A, Needleman H. Lead in milk and infant blood: a dose-response model. Arch Environ Health 1985; 40: 283-286. https://doi.org/10.1080/00039896.1985.10545933

17. Omokhodion FO, Crockford GW. Lead in sweat and its relationship to salivary and urinary levels in normal healthy subjects. Sci Total Environ 1991; 103: 113-122. https://doi.org/10.1016/0048-9697(91)90137-4

18. World Health Organization (WHO). Legally-binding controls on lead paint. 2023. Available at: https://www.who.int/data/gho/data/themes/topics/indicator-groups/legally-binding-controls-on-lead-paint (Accessed on January 10, 2024).

19. Dikme G, Arvas A, Gur E. The relation between blood lead and mercury levels and chronic neurological diseases in children. Turk Ach Pediatr 2013; 48: 221-225. https://doi.org/10.4274/tpa.296

20. Sevinc N, Bilici N, Sevinc E, Dogan E. Blood and faecal lead levels in children with various functional gastrointestinal disorders. An Pediatr (Engl Ed) 2022; 96: 35-42. https://doi.org/10.1016/j.anpede.2021.02.001

21. Adams JB, Holloway CE, George F, Quig D. Analyses of toxic metals and essential minerals in the hair of Arizona children with autism and associated conditions, and their mothers. Biol Trace Elem Res 2006; 110: 193-209. https://doi.org/10.1385/BTER:110:3:193

22. Guo BQ, Li HB, Liu YY. Association between hair lead levels and autism spectrum disorder in children: a systematic review and meta-analysis. Psychiatry Res 2019; 276: 239-249. https://doi.org/10.1016/j.psychres.2019.05.022

23. Iaquinta F, Machado I. Biomonitoring of arsenic, lead, manganese and mercury in hair from a presumably exposed Uruguayan child population. Bioanalysis 2024; 16: 107-116. https://doi.org/10.4155/bio-2023-0157

24. Agency for Toxic Substances and Disease Registry. Toxicological profile for lead. 2020. Available at: https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf

25. Morton J, Carolan VA, Gardiner PHE. Removal of exogenously bound elements from human hair by various washing procedures and determination by inductively coupled plasma mass spectrometry. Anal Chim Acta 2002; 455: 23-34. https://doi.org/10.1016/S0003-2670(01)01578-1

26. Renshaw GD, Pounds CA, Pearson EF. Variation in lead concentration along single hairs as measured by non-flame atomic absorption spectrophotometry. Nature 1972; 238: 162-163. https://doi.org/10.1038/238162a0

27. Schuhmacher M, Domingo JL, Llobet JM, Corbella J. Lead in children's hair, as related to exposure in Tarragona province, Spain. Sci Total Environ 1991; 104: 167-173. https://doi.org/10.1016/0048-9697(91)90070-u

28. Vigeh M, Yokoyama K, Matsukawa T, Shinohara A, Ohtani K, Shariat M. Hair metal levels and childhood weight gain. Iran J Public Health 2020; 49: 1510-1519. https://doi.org/10.18502/ijph.v49i8.3895

29. Tippairote T, Temviriyanukul P, Benjapong W, Trachootham D. Prevalence and factors associated with high levels of aluminum, arsenic, cadmium, lead, and mercury in hair samples of well-nourished Thai children in Bangkok and perimeters. Biol Trace Elem Res 2019; 188: 334-343. https://doi.org/10.1007/s12011-018-1435-6

30. Wolfsperger M, Hauser G, Gössler W, Schlagenhaufen C. Heavy metals in human hair samples from Austria and Italy: influence of sex and smoking habits. Sci Total Environ 1994; 156: 235-242. https://doi.org/10.1016/0048-9697(94)90190-2