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ORIGINAL RESEARCH ARTICLE

Risk Factors for Lead Toxicity and its Effect on Neurobehavior in Indian Children

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Abstract Lead (Pb) is profoundly used heavy metal despite its known toxic effects. Children in particular are more susceptible to Pb toxicity. Thus, the present study was carried out to estimate the prevalence of lead toxicity in Indian children, to observe serum levels of biochemical parameters and to evaluate psychopathological implications of Pb toxicity using population specific scale—Childhood Psychopathological Measurement Schedule (CPMS) in children. Children between 9 and 15 years of age were included in the study (N = 70). Demographic details and information regarding the source of lead exposure were collected using a self-made questionnaire. All biochemical investigations were performed in Beckman Coulter Auto-analyser AU680 and Blood Lead Levels (BLL) were estimated by Graphite Furnace Atomic Absorption Spectrophotometer. The neurobehavioral state of the children was assessed by a population-specific scale i.e., CPMS, which evaluates for neurobehavior under 8 factors, titled, Low intelligence with behavioural problems, Conduct disorder, Anxiety, Depression, Psychotic symptoms, Special symptoms, Physical illness with emotional problems, and Somatization. The median BLL of the study population was 4.9 µg/dL. Habit of frequently consuming roadside food, proximity of residence to vehicular traffic and educational status of the mother were observed to be significant contributing factors for high BLL (≥ 5 µg/dL). Serum alkaline phosphatase (P = 0.02) and phosphorous levels (P = 0.04) were significantly lower in children belonging to high BLL group. A significantly high adverse neurobehavioral score was observed in high BLL group children compared to low BLL group ($P < 0.05$). There was high prevalence of Pb toxicity with 50% of children having BLL > 5 µg/dL. Further, certain lifestyle characteristics such as proximity of residence to vehicular traffic, frequent consumption of roadside food and lower educational status of the mother could be possible risk factors for higher Pb exposure in children. Evaluation of neurobehavior in children with high BLL revealed a high prevalence of adverse neurobehavior in them when compared to children in low BLL group.

Keywords Lead · Children · Neurobehavior · India

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Introduction

Metal toxicities contribute substantially to the global health burden, owing to robust industrialization [1]. Lead (Pb) is one such heavy metal known to exert a significant toxic

effect on all age groups [2]. The nature of toxicity varies with concentration, route, duration, age of exposure, cultural and ethnic differences [3]. Adults exposed to high lead concentrations (> 40 µg/dL) are susceptible to a wide spectrum of disorders ranging from generalized fatigue and headache to increased risk of hypertension and renal dysfunction [4, 5]. However, no level of Pb is safe in children, as children are susceptible to irreversible neurodevelopmental alterations even at low blood lead concentrations (< 10 µg/dL) [6].

The impact of Pb on various developmental aspects have been studied in young and adolescent children, including the impact of prenatal exposure [2]. The adverse impact of Pb on the neuronal system is significant with neuronal plasticity and the serotonergic system being significantly impaired during early development [7, 8]. Lead toxicity in children is associated with poor scores in IQ (Intelligence Quotient) test, delayed reaction time, attention deficit and increased risk of autism spectrum disorders [2]. Data from American and European countries when compared to Indian studies, indicate a high prevalence of Blood Lead Levels ≥ 5 µg/dL in Indian children. [9–11]. Stringent measures have been employed to curb lead pollution, such as, abolition of leaded petrol and restriction of allowable lead levels in paints and water sources. Despite continued efforts, lead toxicity remains to be a major public health concern. The Institute of Sanimetry and Health Assessment (IASH) in 2016 reported 63% of idiopathic intellectual development failure and 10% global burden of hypertensive heart disease to be due to lead toxicity [12].

Occupational exposure is common among adults, whereas children are more commonly exposed to Pb from lead-containing water, cooking utensils, toys, cosmetics, ornaments, folk/ayurvedic medicines etc. High exploratory activity, hand-mouth behaviour and greater absorption rates of ingested Pb further enhance the risk of toxicity in children [13, 14]. Unlike other trace elements, Pb has no beneficial role in the body [12]. With exposure, Pb remains in circulation with a half-life of 40 days, following which it is deposited in calcified tissues and re-enters circulation with bone resorption [15].

Pb can cause an imbalance in calcium (Ca) metabolism and thereby, affect bone mineralization and other cellular pathways mediated by calcium. Pb competes with calcium at intestinal absorption sites, at binding sites on calmodulin and with calcium phosphate complexes at sites of bone mineralization. Calmodulin is a Ca receptor widely present on cells associated with Ca mediated signalling pathways. Interference of Pb in Ca homeostasis has been implicated to mediate the wide range of toxic effects observed in Pb toxicity. Further, children deficient of Ca, vitamin D and other micronutrients like zinc, iron have been reported to be more vulnerable for Pb toxicity [16, 17].

Only limited studies exist on the neuropathological impact of childhood Pb exposure among Indian children; in particular, lacking neurobehavioral evaluation by population-specific standardized scale. Jodhpur harbours several small-scale industries engaged in Pb and other heavy metal works such as handicrafts, textile and dye industries. Also, previous studies in Jodhpur have reported a prevalence of high Blood Lead Level (BLL) among adults and occupational workers [14, 18]. Therefore, the present study was carried out to estimate the extent of childhood lead toxicity (BLL > 5 µg/dL) in the study population, to understand the impact of lead toxicity on neurobehavior using a population-specific scale—Childhood Psychopathological Measurement Schedule (CPMS) and possibly define a 'neurobehavioral signature' associated with childhood lead toxicity in Indian children.

Materials and Methods

Study Sample

The study population consisted of children between the age group of 9–15 years. A previous study conducted in Jodhpur and NHANES survey of 1999–2002 reported prevalence of high blood lead level to be 5% [18, 19]. Based on this, the sample size for the present study was calculated to be 70. Ethical clearance was obtained from the Institutional Ethics Committee prior to subject recruitment. The study was a cross-sectional study with a single time assessment of biochemical parameters, BLL and neurobehavior. Study subjects were enrolled from schools in the Basni area of Jodhpur, Rajasthan. Demographic details, neurobehavioral assessment and blood sample were acquired from the subjects at their respective schools. A total of 70 children with informed consent from parent/guardian were included in the study. Socio-demographic details of the children were noted from the parent/guardian using a self-developed questionnaire. The neurobehavioral assessment was carried out by use of the Childhood Psychopathological Measurement Schedule (CPMS) and venous blood samples was collected for blood lead and other biochemical investigations. Blood calcium, phosphorus, albumin, globulin, and alkaline phosphatase (ALP) estimations were performed on the same day and samples were stored at − 20 °C until further use.

Neurobehavioral Assessment

Neurbehaviour of the children was assessed by Childhood Psychopathological Measurement Schedule (CPMS). It was adapted from Achenbach Child Behaviour Check List (CBCL) and standardized for use in Indian children [20]. It

was developed as a screening tool for assessment of neurobehavior in children (4–14 years). It comprises 75 questions assessing negative symptoms of neurobehavior under eight factors i.e., low intelligence with behavioural problems, conduct disorder, anxiety, depression, psychotic symptoms, special symptoms, physical illness with emotional problems and somatization. Each question has a 'Yes' or 'No' response carrying 1 or 0 scores, respectively, pertaining to whether a symptom is present. A score of more than 10 is suggested to be associated with psychopathological disorders in children. Questions were directed to the parent/guardian of the child and responses were recorded simultaneously.

Biochemical Investigations and Blood Lead Analysis (BLL)

Venous blood samples were collected in lead-free EDTA vacutainers for whole blood (lead estimation) and gel containing serum separator tubes for serum samples (biochemical parameters), by venepuncture. All biochemical investigations were performed in Beckman Coulter Autoanalyser AU680 following adequate quality control at the Clinical Biochemistry laboratory, AIIMS, Jodhpur. Total protein was estimated by the Biuret method, albumin was determined by the bromocresol green method, total calcium was determined by Arsenazo III method, phosphorous by phosphomolybdate method and alkaline phosphatase (ALP) by p-nitro-phenylphosphate (pNPP) in the presence of 2-amino-2-methyl-1-propanol (AMP) (PNPP AMP Buffer) method.

BLL was estimated using Graphite Furnace Atomic Absorption Spectrophotometer (GFAAS) with Zeeman correction in ICE 3500 system (Thermofisher Scientific, Waltham, MA) after warranting proper quality control. Matrix modifier (0.2% HNO_3, 0.5% Triton X-100 and 0.1% Diammonium Hydrogen Phosphate) was used to prepare standards and samples. Calibration standards were prepared from serial dilutions of stock solution (1000 ppm Pb). A five-point calibration curve was made with 0, 2.5, 5, 10 and 20 ppb of Pb. CLIN Check Whole Blood Control level I (54.5 µg/L), II (219 µg/L) and III (425 µg/L) (Recipe, Germany) were used as quality control. Samples were estimated at 20 times dilution using 0.2% HNO_3 as diluent. Absorbance was measured at 283.3 nm and results are expressed as µg/dL. The limit of detection (LOD) was 0.12 µg/dL and limit of quantification (LOQ) was 0.36 µg/dL.

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism version 8.3. Numerical values were expressed in terms of mean, median and range. The normality of data assessed by the Shapiro–Wilk test showed non-parametric distribution. Therefore, the correlation between BLL and biochemical parameters were analysed using the Spearman correlation test. Comparison between High BLL and Low BLL groups were carried out by the Mann–Whitney U test. P value < 0.05 was considered to be significant.

Results

Demographic Details

A total 70 school going children between age of 9–15 years were included in the study. Majority of the children fell between age of 13–15 years (N = 60). The male/ female ratio of the children was 0.9. The median BLL was 4.9 µg/dL, and 15% (N = 11) of them had BLL > 10 µg/dL. Distribution of BLL in the study participants are depicted in Fig. 1.

Potential Risk Factors for Pb Exposure in Children

Among the various lifestyle characteristics evaluated as potential risk factors for Pb exposure in the current study population, habit of frequently consuming roadside food, proximity of residence to vehicular traffic and educational status of the mother were observed to be significant contributing factors. The odds of children frequently consuming roadside food to have high BLL was significantly higher than their counterpart (OR = 5.7, P = 0.01), similarly children who resided close to vehicular traffic had significantly higher odds of having higher BLL compared to those living far from traffic (OR = 3.55 P = 0.49). Educational status of the mother was also observed as a significant risk factor for BLL, as children of illiterate

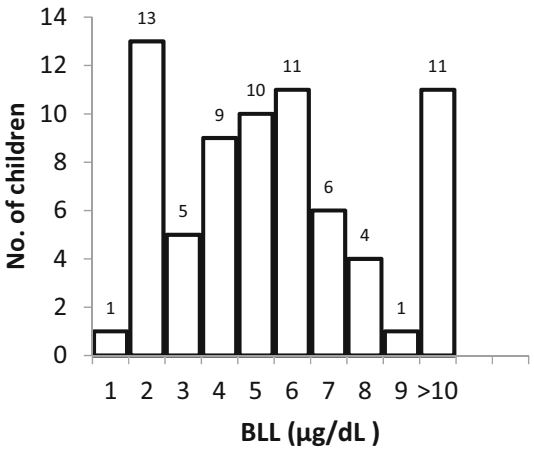

Fig. 1 Histogram depicting distribution of BLL in the study participants

Table 1 Association of BLL with potential risk factors (chi-square test)

S No	Risk factors	N	BLL (μg/dL) Mean (± SD)	Children with BLL > 5 (%)	Odds Ratio (95% CI)
A	Personal habits				
1	Habit of washing hands before food				
	Yes	54	5.5 (± 4.1)	25	0.63 (0.20 to 1.8)
	No	16	5.6 (± 4.1)	10	
2	Habit of frequently eating roadside food (> 3 times/week)				
	Yes	28	5.2 (± 3.6)	22	5.7* (2–16.2)
	No	42	5.7 (± 4.4)	13	
3	Habit of using sindoor/surma				
	Yes	10	4.49 (± 3.36)	4	0.44 (0.11 to 1.60)
	No	60	6.7 (± 7.11)	31	
4	Habit of using traditional medicine				
	Yes	26	8 (9.79)	12	0.7 (0.26 to 1.82)
	No	44	5.3 (3.23)	23	
5	Owning pets at home				
	Yes	10	5.6 (± 3.5)	5	1.29 (0.31 to 5.27)
	No	60	5.5 (± 4.2)	30	
6	Playing with coloured toys				
	Yes	22	4.9 (± 3.6)	8	0.44 (0.15 to 1.35)
	No	48	5.8 (± 4.3)	27	
B	Housing conditions				
1	Residence located close to vehicular congestion (< 2 km)				
	Yes	55	5.3 (± 3.7)	11	3.55* (1.0–12.5)
	No	15	6.4 (± 5.4)	24	
2	Residing in old house (Constructed > 5 years)				
	Yes	56	6.8 ± 7.35	27	0.69 (0.21–2.27)
	No	14	4.66 ± 3.1	8	
3	History of recent painting (< 2 years)				
	Yes	29	7.29 ± 5.14	21	1 (0.38–2.60)
	No	41	5.79 ± 7.71	14	
C	Parent characteristics				
1	Education status of father				
	No formal education	6	6.9 ± 5.14	6	7.03 (0.79–61.8)
	Any formal education	64	6.37 ± 6.93	29	
2	No separate clothes for work				
	Yes	23	5.83 ± 0.21	20	0.39 (0.14–1.11)
	No	47	5.55 ± 1.88	15	
3	Education status of mother				
	No formal education	30	4.22 ± 2.4	24	3.63* (1.39–9.4)
	Any formal education	40	8.06 ± 8.36	11	
4	Use of cosmetics by mother				
	Yes	60	5.6 (± 4.03)	29	0.81 (0.22–2.93)
	No	10	5.2 (± 4.9)	6	

*P value < 0.05 was considered to be significant

mothers had 3.63 times greater odds of having high BLL (Table 1).

Biochemical parameters

Total protein, albumin and globulin were estimated in the study participants as means to assess nutritional status and calcium, phosphorus and ALP were measured to assess bone health. Median levels of all the studied biochemical parameters fell within the normal reference ranges. A correlational analysis between BLL and the studied biochemical parameters showed a significant direct relationship of BLL with calcium and an indirect association with phosphorous levels (Table 2). Further, when the study participants were divided into high and low BLL groups based on median BLL (4.9 µg/dL), a significant difference was observed in the median values of total protein, albumin, alkaline phosphatase and phosphorous levels. While total protein and albumin were significantly higher in High BLL group, ALP and phosphorous were significantly lower in High BLL group (Table 3).

Pb and Neurobehaviour

A scatter plot of CPMS scores of each factor against BLL showed an increasing trend with an increase in BLL, suggestive of increase in adverse neurobehavior with increasing BLLs (Fig. 2). Further when CPMS scores were compared between high and low BLL group, mean CPMS scores were significantly higher in High BLL group when compared to the low BLL group across several factors (Fig. 3). The odds of children with high BLL (> 5 µg/dL) having a CPMS score more than 10 was estimated to be 25, (95% CI = 3.07–203.2), indicating a very high risk for adverse neurobehavior among children with high BLLs (Data not shown).

Discussion

Pb is one of the most studied heavy metal toxicants that is known to cause adverse effects in children. Regulations imposed to restrict Pb usage have reduced its levels globally, nevertheless, Pb toxicity continues to be a major public health concern [21]. Awareness among the common public, especially parents and teachers can play a pivotal role in the successful prevention of childhood lead toxicity. BLLs of Indian children have been reported to be to be greater than in children in other countries and a similar finding was observed in the present study as well [9–11, 22]. Previous studies have reported lifestyle factors such as residence close to vehicular traffic, use of unfiltered water and old houses as potential source for Pb exposure, in our study the habit of frequently consuming roadside food, proximity of residence to vehicular traffic and lower educational status of the mother appeared to be significant contributing factors for high blood Pb levels [23]. History of recent painting might contribute to Pb exposure in children as paints in India continue to have high lead levels. Bureau of Indian Standards (BIS) regulation of Pb levels in paint is a voluntary and not mandatory

Table 2 Correlation between biochemical parameters and blood lead level in the study subjects (N = 70)

Analyte	Mean ± SD	Median (IQR)	r (*P* value)
Total Protein (g/dL)	7.5 ± 0.55	7.46 (0.73)	0.31 (0.07)
Albumin (g/dL)	4.4 ± 0.29	4.4 (0.2)	0.31 (0.07)
Globulin (g/dL)	3.15 ± 0.47	3.09 (0.5)	0.14 (0.22)
ALP (U/L)	196.36 ± 110.15	178.5 (157)	−0.19 (0.10)
Calcium (mg/dL)	9.57 ± 0.46	9.61 (0.66)	0.25 (0.03)
Phosphorous (mg/dL)	4.1 ± 0.80	4.05 (1.2)	−0.35 (0.001)

r: Spearman's correlation coefficient; P < 0.05 was considered significant

Table 3 Comparison of biochemical data between high and low BLL groups:

Parameter	High BLL (N = 35)		Low BLL (N = 35)		*P* value
	Mean ± SD	Median	Mean ± SD	Median	
Total Protein (g/dL)	7.63 ± 0.49	7.6 (0.65)	7.29 ± 0.49	7.39 (0.67)	0.01
Albumin (g/dL)	4.47 ± 0.28	4.43 (0.4)	4.3 ± 0.26	4.33 (0.2)	0.01
Globulin (g/dL)	3.22 ± 0.48	3.17 (0.48)	3.10 ± 0.55	3.03 (0.76)	0.16
ALP (U/L)	172.8 ± 100.7	125.5 (127)	229.9 ± 126.8	231 (172)	0.04
Calcium (mg/dL)	9.62 ± 0.42	9.63 (0.59)	9.45 ± 0.44	9.49 (0.66)	0.12
Phosphorous (mg/dL)	3.9 ± 0.80	3.85 (0.97)	4.40 ± 0.78	4.41 (1.11)	0.02

P value are result of Mann Whitney U test and value < 0.05 was considered to be significant

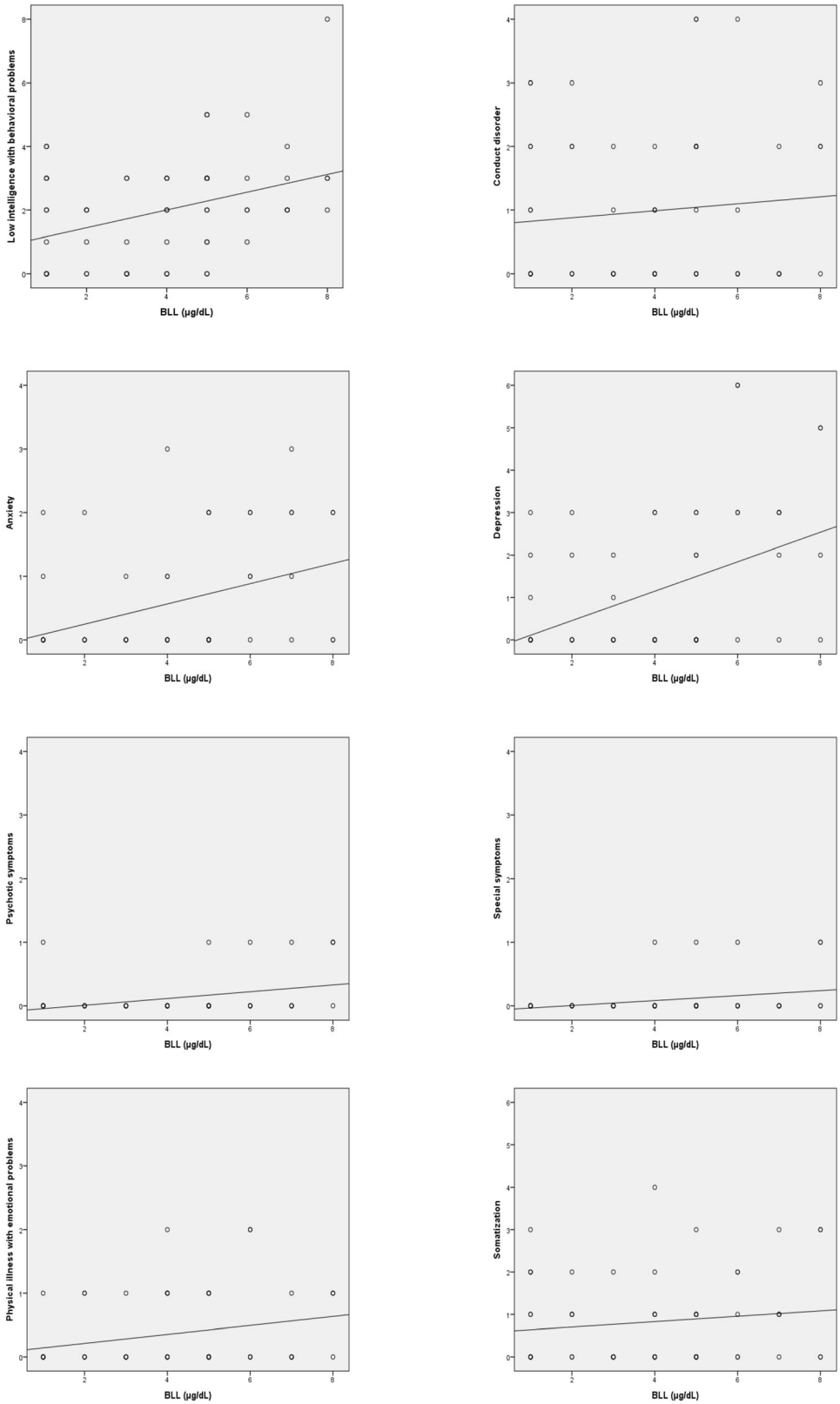

Fig. 2 Scatter plot relating blood lead level (BLL) to eight neurobehavioral factors assessed by childhood psychopathological measurement schedule (CPMS)

requirement and paints commonly used continue to have high Pb levels [24]. However, history of recent painting or the absence of it did not increase the odds for high BLL in the present study.

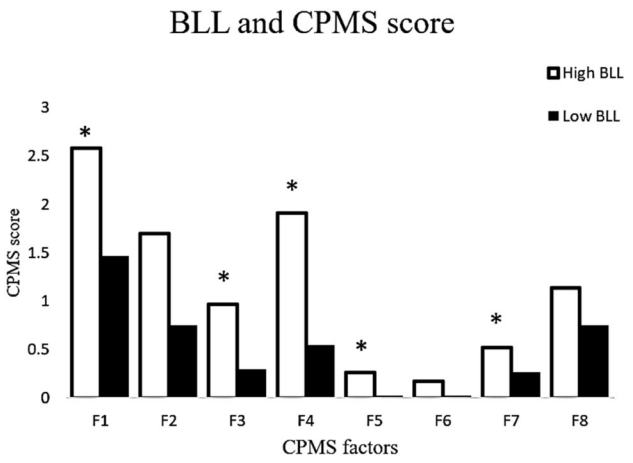

Fig. 3 Results of Man Whitney U Test comparing scores of childhood psychopathological measurement schedule (CPMS) factors between high BLL group and low BLL group. *P value < 0.05. F1 = Low intelligence with behaviour problems, F2 = Conduct disorder, F3 = Anxiety, F4 = Depression, F5 = Psychotic symptoms, F6 = Special symptoms, F7 = Physical illness with emotional problems, F8 = Somatization

Nutritional status in children have been reported to influence the absorption and retention of Pb in the body. In particular dietary deficiency of calcium, phosphorous, iron and zinc may increase Pb absorption and retention [25]. In the present study, a significant association was observed between BLL, serum total calcium and phosphorous levels. While serum calcium had a mild significant positive association (P = 0.03, r = 0.25), serum phosphorous had a moderate negative association (P = 0.001, r = − 0.35) with BLL, respectively. Results from previous studies are ambiguous with both decrease and increase in calcium levels with BLL. Dobrakowski et al. reported an increase in serum calcium levels post short-term Pb exposure and have suggested a competitive displacement of calcium from its binding sites by Pb [26]. Further, a possibility of Pb mediated activation of intracellular reactive oxygen system and increase in intracellular calcium levels with subsequent decrease in serum calcium levels have also been suggested in previous studies [27, 28]. Further, Pb may replace calcium in calcium phosphate required for effective bone mineralization and affect mineralization of bones in children [25]. In addition to calcium and phosphorous, serum alkaline phosphatase enzyme required for effective bone mineralization was also found to be significantly lower in high BLL group when compared to children of low BLL group (P = 0.02). Although the median calcium, phosphorous and alkaline phosphatase levels were within reference range in both high and low BLL group, a significant difference in their levels between the two groups suggests a possibility of Pb mediated effect on these bone health markers.

In addition to skeletal system, central nervous system (CNS) is well documented to be critically affected in childhood Pb toxicity. In our study, a significant direct relationship was observed between BLL and scores of Intelligence and behavioural problems evaluated by Factor I of CPMS. This finding was in correspondence with previous studies that reported low IQ and ADHD like symptoms in childhood Pb toxicity [29].High BLL (≥ 5 µg/dL) in childhood can impair neurodevelopment and adversely affect Intelligence Quotient (IQ), attention span and increase the risk of ADHD spectrum of disorders. Impact on IQ studied using Wechsler Intelligence Scales indicated a clear negative effect on both performance and verbal IQ [30]. Longitudinal studies have also shown lower IQ levels in adults with high lead levels in early childhood [31]. Behavioural changes are another adverse effect of Pb on CNS. Studies have reported a prevalence of both internalising and externalising behaviour among children [32].In the present study, children showed increased tendency of social withdrawal and excessive worrying with increasing BLLs. Internalizing behaviour such as depression, anxiety, loneliness etc. hinder holistic mental development in children as they deter their normal social experience associated behavioural development. Scores of Factor 3 and 4 relating to anxiety and depression were significantly higher in high BLL group ($P < 0.05$).

Negative effects of Pb on neuronal development have been studied in relation to its influence on calcium channels, NMDA receptors, serotonergic and GABAnergic system [4]. As the present study is cross-sectional in nature, the effect of chronic Pb toxicity on neurobehavior from early childhood exposure could not be accounted for in the present study. Further, anthropometric measurements such as height and weight would serve as better markers to evaluate nutritional status and thus their impact on vulnerability to Pb toxicity in children. Nevertheless, the findings from the present study suggest the prevalence of Pb associated skeletal and behavioural abnormality in Indian children with high BLLs. Limitation of the present study would be the small sample size and cross-sectional study design. A large-scale cohort study assessing possibility of prenatal lead exposure and its impact on late childhood would present a more comprehensive picture of childhood Pb toxicity in Indian children.

Conclusion

Only few studies have assessed the nutritional, biochemical and neurotoxic effect of lead in Indian children and to the best of our knowledge this is the first study to utilise a neurobehavioral scale standardized and validated for Indian population. Findings from present study suggest a

possible prevalence of Pb associated neurotoxicity in Indian children. In addition to neurobehavioral effects, skeletal growth in children might also be affected by Pb toxicity and maintenance of adequate nutrition might reduce the vulnerability to lead toxicity in children.

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Availability of data and material Data and materials of the study are available on request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This study involves the participation of human subjects with the approval from the Institutional Ethical Committee (IEC), All India Institute of Medical Sciences, Jodhpur, Rajasthan India. (AIIMS/IEC/2018/640). The study was performed in accordance with down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Prior written informed consent was obtained from all subjects recruited in this study.

Consent for publication All authors provide consent for publication.

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