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Preliminary study of urinary arsenic concentration and arsenic methylation capacity effects on neurodevelopment in very low birth weight preterm children under 24 months of corrected age

Chuen-Bin Jiang, MD[a,b], Yu-Mei Hsueh, PhD[c,d], Guang-Lin Kuo, MS[e], Chyong-Hsin Hsu, MD[f], Jui-Hsing Chang, MD[b,f,g], Ling-Chu Chien, PhD[e,h,*]

Abstract

The neurological prognoses of very low birth weight preterm (VLBWP) children during the first 2 years of life will influence their neurodevelopment during subsequent childhood years and adolescence. The objective of this study was to systemic investigate relationships of urinary arsenic (As) concentrations, the As methylation capability, and toenail As concentrations on cognitive, language, and motor development in VLBWP children under 24 months of corrected age.

Participants (n = 60) in our study were recruited from October 2010 to April 2013. Urine and toenail samples were collected for evaluation to assess As exposure. The Bayley scales of infant development III were used to evaluate neurodevelopment at 2 years of corrected age. Concentrations of As species in urine and the As concentration in toenails were, respectively, analyzed using HPLC-HG-AAS and ICP-MS.

The mean concentration of total As was 28.6 μg/g creatinine, and inorganic As was 1.01 μg/L in urine. The urine contained an average of 3% inorganic As, 2% monomethylarsonic acid, and 95% dimethylarsinic acid (DMA). The mean concentration of As in toenails was 225 ng/g. Children with a longer gestational age (≥28 weeks) and higher DMA % levels appeared to have the highest unadjusted cognitive and fine motor scores.

Our study results suggest that gestational age is associated with neurodevelopment in VLBWP children. We recommend that further study simultaneously analyze multiple environmental contaminants that may have adverse effects on neurodevelopment, use biomarkers for the mother–child pair, and determine whether prenatal or postnatal As exposure has a greater influence on the neurological development of VLBWP children.

Abbreviations: As = arsenic, As^{III} = Arsenite^{III}, As^{V} = Arsenite^{V}, Bayley-III = the Bayley Scales of Infant and Toddler Development, DMA^{V} = Dimethylarsonic acid, HPLC-HG-AAS = high-performance liquid chromatography with a hydride generator and atomic absorption spectrometer, iAs = inorganic As, ICP-MS = inductively coupled plasma mass spectrometry, MMA^{V} = monomethylarsonic acid, nAs = Toenail total As level, NIST = National Institute of Standard Technology, Pb = lead, PMI = primary methylation index, SD = standard deviation, SE = standard error, SMI = secondary methylation index, TUAs = total urinary as level, VLBWP = very low birth weight preterm.

Keywords: arsenic methylation capability, gestational age, neurodevelopment, very low birth weight preterm children

Editor: Babak Abdinia.

This work was supported by a grant (TMU102-F-002) from Taipei Medical University.

Conflict of Interest Statement: The authors have disclosed all financial and interpersonal relationships that could present a potential conflict of interest.

[a] Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, MacKay Children's Hospital, [b] Mackay Junior College of Medicine, Nursing and Management, Taipei, [c] Department of Family Medicine, Shuang Ho Hospital, [d] Department of Public Health, School of Medicine, College of Medicine, [e] School of Public Health, College of Public Health, Taipei Medical University, [f] Division of Neonatology, Department of Pediatrics, MacKay Children's Hospital, Taipei, [g] MacKay Medical College, New Taipei City, [h] Nutrition Research Center, Taipei Medical University Hospital, Taipei, Taiwan.

[*] Correspondence: Ling-Chu Chien, School of Public Health, Taipei Medical University, Taipei, Taiwan, Nutrition Research Center, Taipei Medical University Hospital, Taipei, Taiwan, 250 Wuxing Street, Xinyi District, Taipei 11031, Taiwan (e-mail: lcchien@tmu.edu.tw).

Medicine (2018) 97:43(e12800)

Received: 7 December 2017 / Accepted: 19 September 2018

http://dx.doi.org/10.1097/MD.0000000000012800

1. Introduction

Children, compared to adults, may experience higher exposure to environmental contaminants because of early life stage behaviors and physiology.[1] Arsenic (As) is a neurotoxicant that can alter cognitive function, particularly in children. One study indicated that children exposed to As and lead (Pb) have impaired central nervous system functions, including poorer performance on long-term memory and attention assessments.[2] A cross-sectional study found that long-term As exposure in drinking water led to cognitive deficits among adolescents in Taiwan.[3] Hafeman et al[4] reported an association between As concentrations and subclinical sensory neuropathy in Bangladesh. Water, urinary, and toenail As concentrations were shown to be inversely related to motor function scores among 304 children aged 8 to 11 years.[5] Hsieh et al[6] found that the As methylation capacity is associated with developmental delay among children in Taiwan. Those findings suggest that As exposure may cause neuro-developmental damage.

A body of evidence suggests that methylation of inorganic (i) As is a detoxification mechanism.[7,8] As^V is readily reduced to As^{III}[9] and is subsequently methylated to monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V).[10,11] Approximately 55% to 80% of environmentally exposed As is excreted in urine within 3 to 4 days after being metabolized.[12,13] The As methylation capacity may particularly confer a higher risk of developmental disorders in children, as they demonstrate a poorer methylation capacity compared to adults.[14,15] Toenail clippings have been used to assess biomarkers to evaluate the long-term As exposure[16] because of the nails' growth rate of 0.03 to 0.05 mm/day and outgrowth in 12 to 18 months.[17]

Very low birth weight (birth weight <1500 g) preterm (gestational age <37 weeks) (VLBWP) children are at risk of cognitive deficits, growth delays, and academic underachievement compared to those born at term and with a normal birth weight.[18–20] There are more than 200,000 newborn babies in Taiwan each year, and the incidence of prematurity is about 8% to 10%.[21] Consequences of growth lags persist not only in the neonatal period but also throughout childhood[22–24] and adulthood. The neurological prognoses of VLBWP children during the first 2 years will influence their neurodevelopment during subsequent childhood years and adolescence.

VLBWP children are at increased risk for developmental impairments.[25–27] However, studies on both preterm effects and postnatal As exposure of children are limited. To the best of the authors' knowledge, consistent evidence of relationships between As exposure and neurodevelopment in the early life of VLBWP children has not yet been well established.

Consequently, one of the aims of this study was to investigate relationships of cognitive, language, and motor development at 24 months of corrected age with As concentrations, the arsenic methylation capability, and As concentrations in various biomarkers, including the urine and toenails. The Bayley Scales of Infant and Toddler Development (Bayley-III) were calculated and validated at 6, 12, and 24 months of corrected age. The effects of variables such as gestational age and urinary As species on children's cognitive, language, and motor development at 24 months of corrected age were then better elucidated. Therefore, it is crucial to investigate the VLBWP As exposure in children, particularly in the critical early life stage, and develop optimal strategies to reduce later health effects in school-aged and adolescent children.

2. Materials and methods

2.1. Study subjects

Mackay Memorial Hospital and other nonprofit organizations jointly founded the premature baby foundation of Taiwan and provide follow-up programs for those born very prematurely or at very low birth weight of <1500 g after discharge from newborn intensive care units. Children were enrolled in this study who attended the program if they met the following criteria: a birth weight of ≤1500 g and a gestational age of <37 weeks; neurodevelopment completely evaluated at 6, 12, and 24 months of corrected age; and both urine and toenail samples collected at 24 months of corrected age. In total, 60 children were recruited from Taipei MacKay Memorial Hospital between October 2010 and April 2013. Urine and toenail samples of children were collected and served as biomarkers of internal dose indices of As exposure. A structured questionnaire was administered by a trained interviewer to obtain demographic information of participants and their parents. Sociodemographic characteristics of both the mother and father were collected. Information pertaining to the children's sociodemographic characteristics (e.g., sex, gestational age, weight, head circumference, height, and Apgar scores at birth), dietary intake (e.g., rice, meat, fish, shellfish, eggs, dairy, vegetables, and fruit), parity, and family income data were also collected. This work was approved by Taipei Mackay Memorial Hospital (13MMHIS088). Written informed consent was prepared for both parents of participating infants. All of parents provided written informed consent before beginning the study.

2.2. Urinary As profiles and nail As concentration assessments

Urine samples were collected from each participant to analyze As^{III}, DMA^V, MMA^V, and As^V profiles as measured by high-performance liquid chromatography with a hydride generator and atomic absorption spectrometer (HPLC-HG-AAS) according to previously published methods.[28] Standard reference material (SRM 2670a) from the National Institute of Standard Technology (NIST) was used to assess the precision and accuracy of the urinary As analyses. Recovery rates of As^{III}, DMA^V, MMA^V, and As^V ranged 93.8% to 102.2% using the following equation: ([sample spiked standard solution concentration − sample concentration]/standard solution concentration) × 100. Detection limits of the 4 arsenic species were 0.02, 0.08, 0.05, and 0.07 μg/L, respectively. All urinary As species were adjusted to urinary creatinine. The sum of As^{III} and As^V was referred to as iAs. The sum of As^{III}, As^V, MMA^V, and DMA^V was referred to as the total urinary As concentration. Percentages of each As species (iAs %, MMA^V %, and DMA^V %) were calculated by dividing the concentration of each species by the total As concentration. Primary methylation and secondary methylation indices were calculated as (PMI = MMA^V/iAs) and (SMI = DMA^V/MMA^V), respectively. Percentages of each As species, the PMI, and SMI were internal dose indices of As exposure of the children.

Total As concentrations in toenail samples were determined by inductively coupled plasma mass spectrometry (ICP-MS; Thermo X-series II). Toenail samples were rinsed 3 times with deionized water after sonication with a neutral detergent for 30 min and dried in an oven at 37 °C for 24 hours. Approximately 0.02 g of samples was microwave-digested (Multiwave 3000, Anton-Paar)

with 3 mL of 65% nitric acid (Suprapur, Merck, Kenilworth, NJ). We washed residuals in a Teflon tube with 2% nitric acid and then filtered the digested fluids. Total filtered solutions were stored in 50-mL centrifuge tubes. Certified reference material (CRM GBW 09101b) was used to validate the measurements. The recovery rate ranged 92.1% to 106.6%, with a detection limit of 3.08 ng/g.

2.3. Determination of neurodevelopment

The Bayley Scales of Infant and Toddler Development (Bayley-III) were used to calculate and validate neurodevelopment scores to evaluate the cognitive, language, and motor development at 6, 12, and 24 months of corrected age. All participants were seen by their pediatricians, who assessed their development prior to testing.

2.4. Statistical analysis

Continuous variable distributions are expressed as the mean ± standard deviation (SD). Right-skewed data were normalized by logarithmic transformation for statistical analyses. The Wilcoxon signed-rank test was used to test significant differences in urinary As profiles and toenail As concentrations between extremely preterm children and preterm children. The Kruskal–Wallis test was used to assess significant differences in developmental scores in 4 groups (gestational age [<28 vs ≥28 weeks]) vs DMA % (high vs low). The Wilcoxon rank sum test was conducted to test significant differences in binominal variables. All analyses were performed using the Statistical Analysis Software (SAS) statistical package (SAS, version 9.3, Cary, NC). A P value $< .05$ was considered significant.

3. Results

Table 1 shows demographic characteristics of all enrolled VLBWP children. The mean gestational age of all participants was 28.9 ± 3.3 weeks, and the mean birth weight was 1077 ± 271 g. In total, 68.6% of children were first parity, and the mean maternal age was 32.55 ± 4.34 years. The mean rice and fish intake levels were 19.5 ± 14.5 and 6.1 ± 3.6 servings/week, respectively. The mean length of breast feeding was 4.9 ± 2.8 months. Approximately 87% of families had a monthly family income of ≥US$2300. Urinary As profiles and toenail As concentrations are shown in Table 2. The mean concentration of total As was 28.5 ± 2.72 μg/g creatinine, and iAs was 0.89 ± 0.22 μg/g creatinine in urine. The urine contained mean 2.42% iAs, 1.6% MMA^{v}, and 95.9% DMA^{v}. The primary and secondary As methylation indices were 1.85 and 188, respectively. The mean cumulative As concentration in toenails was 225 ± 15.8 ng/g. Toenail As concentrations were positively correlated with urinary As^{III} ($r = 0.35$, $P < .01$) and urinary total As concentrations ($r = 0.33$, $P < .05$; data not shown).

Comparisons of urinary As profiles and nail As concentrations between extremely preterm and preterm children are shown in Table 3. We divided participants into 2 groups: extremely preterm (gestational age < 28 weeks) and preterm (gestational age ≥28 weeks). We found no significant differences in urinary As profiles or toenail As concentrations between the 2 groups (Table 3). VLBWP children of 6 months of corrected age had lower mean Bayley-III scores in cognitive and fine motor development than those at 12 or 24 months of

Table 1

Sociodemographic and dietary characteristics of very low birth weight preterm children.

Characteristic	All subjects (N = 60) Mean ± SD or %
Children	
Age, months	28.4 ± 6.0
Male	51.7
Female	48.3
Gestational age, weeks	28.9 ± 3.3
Birth length, cm	36.1 ± 4.7
Birth weight, g	1077 ± 271
Head circumference, cm	26.1 ± 2.4
1-min Apgar score	6.6 ± 1.5
5-min Apgar score	8.3 ± 1.0
Parity	
1	68.6
2	27.5
≥3	3.9
Rice intake, servings/week	19.5 ± 14.5
Meat and poultry intake, servings/week	9.3 ± 6.7
Fish intake, servings/week	6.1 ± 3.6
Shellfish intake, servings/week	2.5 ± 2.2
Egg intake, servings/week	6.2 ± 7.4
Dairy intake, servings/week	11.9 ± 17.8
Vegetable intake, servings/week	7.5 ± 7.6
Fruit intake, servings/week	5.9 ± 6.1
Father's age, years	35.3 ± 6.2
Mother's age, years	32.6 ± 4.3
Breastfeeding, months	4.9 ± 2.8
Family income (US$/month)	
<2300	13.3
≥2300	86.7

SD = standard deviation.

Table 2

Urinary As capacity and nail As concentration of very low birth weight preterm children.

Variable	Mean ± SE	Medium	Minimum	Maximum.
Urinary As indices, μg/L				
As^{III}	0.38 ± 0.12	0.01	0.01	3.52
As^{V}	0.05 ± 0.01	0.04	0.04	0.24
MMA^{V}	0.34 ± 0.11	0.03	0.03	4.29
DMA^{V}	12.37 ± 1.56	8.75	1.21	55.84
TUAs	13.14 ± 1.74	9.09	1.28	62.13
Urine creatinine, mg/dL	47.97 ± 4.36	42.85	7.70	167.00
Adjusted urinary As indices, μg/g creatinine				
As^{III}/creatinine	0.76 ± 0.22	0.06	0.01	6.13
As^{V}/creatinine	0.13 ± 0.02	0.09	0.02	0.70
MMA^{V}/creatinine	0.51 ± 0.13	0.17	0.04	5.32
DMA^{V}/creatinine	27.05 ± 2.51	21.44	5.15	87.4
iAs /creatinine	0.89 ± 0.22	0.23	0.05	6.25
TUAs/creatinine	28.46 ± 2.72	22.30	5.26	97.23
As species percentage				
iAs %	2.42 ± 0.43	1.33	0.14	14.03
MMA^{V}%	1.60 ± 0.28	0.78	0.12	8.63
DMA^{V}%	95.98 ± 0.59	97.58	83.34	99.62
As methylation capacity indexes				
PMI	1.85 ± 0.56	0.56	0.02	24.08
SMI	188 ± 28.11	125	9.71	806
nAs, ng/g	225 ± 15.8	208	72.5	560

As = Arsenic, As^{III} = arsenite^{III}, As^{V} = arsenite^{V}, DMA^{V} = dimethylarsonic acid, iAs = inorganic As, Max = maximum, Min = minimum, MMA^{V} = monomethylarsonic acid, nAs = toenail total As level, PMI = primary methylation index, SE = standard error, SMI = secondary methylation index, total As level = $As^{III} + As^{V} + MMA^{V} + DMA^{V}$, TUAs = total urinary As level.

Table 3

Comparisons of urinary As profiles and nail As concentrations between extremely preterm and preterm children.

	Extremely preterm GA <28 weeks (n=29)	Preterm GA ≥28 weeks (n=31)	
Variable	**Mean±SE**	**Mean±SE**	***P* value**
Urinary As indices			
As^{III}, μg/L	0.48±0.25	0.34±0.13	.77
As^{V}, μg/L	0.05±0.01	0.04±0.01	.20
MMA^{V} , μg/L	0.43±0.22	0.30±0.13	.86
DMA^{V}, μg/L	14.8±3.64	11.2±1.54	.61
TUAs, μg/L	15.8±4.04	11.9±1.73	.67
Urine creatinine, mg/dL	48.5±6.77	47.7±5.63	.71
TUAs, μg/g creatinine	31.5±6.13	27.0±2.81	.78
iAs %	2.16±0.66	2.54±0.55	.63
MMA^{V}%	1.38±0.39	1.71±0.37	.86
DMA^{V}%	96.5±0.92	95.8±0.74	.48
nAs, ng/g	203±24.8	237±20.2	.16

As=arsenic, As^{III}=arsenite^{III}, As^{V}=arsenite^{V}, DMA^{V}=Dimethylarsonic acid, GA=gestational Age, iAs=inorganic As, MMA^{V}=monomethylarsonic acid, nAs=toenail total As level, SE=standard error, TUAs=total urinary As level.

Table 4

Results of neurological effects evaluated by Bayley scales of infant and toddler development (Bayley-III) for very low birth weight preterm children at 6, 12, and 24 months of corrected age.

		6 months	12 months	24 months
Score*		**Mean±SD**	**Mean±SD**	**Mean±SD**
Cognitive		7.2±2.7	9.5±3.1	9.1±2.3
Language	Receptive	8.4±2.2	8.0±2.1	9.3±2.1
	Expressive	7.1±2.3	6.9±2.3	8.2±2.7
Motor	Fine motor	7.7±3.5	8.9±2.2	8.8±2.3
	Gross motor	7.8±2.4	7.1±2.8	7.5±2.4

SD=standard deviation.

* Normative score: average, 10,

corrected age (Table 4). The mean gross motor scores for children at 12 and 24 months of corrected age (7.1 and 7.5, respectively) were lower than the cognitive, receptive language, and fine motor scores. We thus attempted to further examine whether an interaction existed between gestational age and As species. Due to the small numbers of subjects, we could not perform a multivariate analysis that included both dichotomized variables. However, children with a longer gestational age (≥28 weeks) and higher DMA % levels appeared to have the highest unadjusted cognitive and fine motor scores (Table 5).

4. Discussion

This is the first study in Taiwan to investigate the impacts of As exposure and relevant risk factors on neurodevelopment at 24 months of corrected age in VLBWP children. We followed the neurodevelopment trends of VLBWP children at 6, 12, and 24 months of corrected age. We found that they had lower mean gross motor development scores before 24 months of corrected age compared to other neurodevelopment scores. Children with a longer gestational age and higher DMA% levels had better cognitive and fine motor scores. However, a risk of As exposure related to neurodevelopment was not observed in this study. But, additional monitoring is still required in the future, especially as the growth lag persists throughout childhood and adulthood.

In Taiwan, Hsieh et al demonstrated that a high urinary total As level (19.69±2.50 μg/L) was significantly associated with the risk of developmental delays in children.[6] A poor As methylation capacity (high MMA^{V} and low DMA^{V}) was significantly negatively associated with the health-related quality of life and functional performance in children with developmental delays. Children exposed to iAs over a long period of time may have decreased intelligence quotient scores.[29] Animal studies have shown that chronic As exposure can induce brain migration and delayed maturation, and is related to motor learning and memory impairment.[30–32] However, the maternal body burden and current exposure are major sources of As for the fetus. In a Mexican Arsenic (BEAR) Pregnancy Cohort study, the authors suggested that maternal urinary iAs was negatively

Table 5

Mean Bayley scales of infant and toddler development (Bayley-III) for very low birth weight preterm children among children with longer or shorter gestational age and higher or lower As apecies levels (dimethylarsonic acid %) at 24 months of corrected age.

	Extremely preterm infants GA <28weeks		Preterm infants GA ≥28 weeks		
Score (mean±SD)	**Low DMA%**	**High DMA%**	**Low DMA%**	**high DMA%**	***P* value***
Cognitive	6.5±2.1	8.1±2.2†	9.5±1.9	9.6±2.2†	.02
Receptive language	6.5±0.7	9.0±1.9	10.0±1.6	9.5±2.2	.09
Expressive language	6.0±0.0	7.6±2.5	8.8±2.9	8.6±2.8	.20
Fine motor	6.0±1.4	7.5±2.0†	9.5±1.2	9.4±2.2†	.006
Gross motor	5.0±2.8	6.8±2.4	9.6±1.8	7.7±2.3	.05

* Kruskal–Wallis test.

† $P<.05$, by the Wilcoxon rank sum test.

As=arsenic, DMA=Dimethylarsonic acid, GA=gestational age, SD=standard deviation.

associated with the gestational age and newborn length.[33] Those authors also found that iAS exposure during the prenatal period may be a source of health effects later in life. Thus, the body of evidence indicates that children exposed to As during prenatal or postnatal periods present with signs of neurobehavioral dysfunction and growth delays.

The placenta is a selective fetal-maternal barrier that is thought to play a role in preventing environmental contaminants from transferring from the mother to the fetus.[34] However, iAs may be able to pass through the placenta and result in preterm births, low birth weights, and stillbirths.[29,35,36] Low-level As exposure during the prenatal period impairs the fetal immune regulation system, potentially causing disease later in life.[37] In a previous Taiwanese study, respective mean Bayley-III scores were 11.4, 12.5, 9.88, 12.9, and 10.4 for cognitive, receptive language, expressive language, and fine motor and gross motor development in full-term children.[38] We found that VLBWP children had lower neurodevelopment scores compared to those of full-term children. Gestational age, weight, head circumference, height, and Apgar 1- and 5-min scores at birth in VLBWP children were positively correlated with Bayley-III scores at 12 and 24 months of corrected age (data not shown). Notably, we could not rule out the possibility that preterm birth was caused by As exposure or co-exposure in mothers during pregnancy.

Arsenic concentrations in the urine and toenails in the present study were comparable to those found in other studies. The mean total As concentration was 13.14 (range: 1.28–62.1) μg/L in urine and 225 ± 15.8 (range: 72.5–560) ng/g in toenails in the present study. In Bangladesh, urinary total As concentrations were 66 and 34 μg/L in 1.5-year-old children who were exposed to As-contaminated drinking water.[39,40] Urinary total As concentrations in Taiwan were 19.69 and 10.22 μg/L in children with and without developmental delays, respectively.[6] Davis et al showed that the median As concentration in infant toenails was 60 (range: 1–1210) ng/g and asserted that As concentrations in infant toenails are a reliable indicator and can serve as a reflection of As exposure from maternal water and dietary sources during the critical window of gestation.[41]

The As methylation capacity decreases with a high MMA% in urine and is related to increased cancer risk, systemic disease, and developmental delays.[6,42] In the present study, we observed low urinary (13.14 μg/L) and toenail As concentrations (225 ng/g) and high DMA% (96%) in VLBWP children. Toenail As concentrations were significantly positively correlated with urinary total As concentrations in the present study. Arsenic methylation is affected by age, sex, race, socioeconomic status, smoking, drinking, exposure route, As species, lifestyle, and dietary habits.[43–46] Children who consume folate, meat, eggs, red-orange vegetables, and green leafy vegetables may have higher As methylation capacities.[45] Measuring toenail As concentrations represents an integrated, reliable, and long-term biomarker for exposure sources. We found that toenail As concentrations were negatively associated with egg ($r = -0.34$, $P < .05$) and dairy intake ($r = -0.40$, $P < .05$; data not shown). Eggs had the highest total choline concentration,[47] which may increase the As methylation capacity.

In the present study, we demonstrated that gestational age was positively associated with receptive communication as well as fine and gross motor development scores at 24 months of corrected age. There is evidence that preterm or extremely preterm children are at risk for cognitive deficits, growth delays, academic underachievement, and behavioral problems.[18–20] With regard to Bayley-III scores, gestational age was the most important risk factor for health effects in life in VLBWP children with low-level As exposure.

This study was a longitudinal study: urinary and toenail samples, and neurodevelopment scores were collected from VLBWP children at 6, 12, and 24 months of corrected age. However, we did not investigate other potential environmental contaminants, such as Pb, cadmium, or polychlorinated biphenyls, that also may have adverse effects on neurodevelopment.[48–50] Additionally, the number of participants was small, and a lack of recruitment of full-term children is a weakness of this study. We did not collect infant toenails, which are highly indicative of maternal As exposure during gestation.[41] Thus, additional research is necessary to determine whether prenatal or postnatal As exposure has a greater influence on neurological development in VLBWP children.

5. Conclusion

In conclusion, to the best of our knowledge, this is the first study analyzing low-level urinary total As, high MMA^V%, and low DMA^V% in VLBWP children in Taiwan. We find that they had lower mean gross motor development scores before 24 months of corrected age compared to other neurodevelopment scores. Our results suggest that gestational age is associated with neurodevelopment in VLBWP children, even without obvious As exposure. Children with a longer gestational age (≥28 weeks) and higher DMA % levels appear to have the highest unadjusted cognitive and fine motor scores. However, this study is cross-sectional in design without a full-term control group and includes only a small number of participants. Larger sample sizes are needed to investigate neurodevelopment in future studies.

Acknowledgments

The authors express their gratitude to staff at the Department of Pediatrics, MacKay Children's Hospital, who assisted with data collection, and all participants in this study for their time and effort.

Author contributions

Conceptualization: Chuen-Bin Jiang, Ling-Chu Chien.
Data curation: Chyong-Hsin Hsu, Jui-Hsing Chang.
Formal analysis: Guang-Lin Kuo, Chyong-Hsin Hsu.
Investigation: Yu-Mei, Hsueh, Guang-Lin Kuo, Chyong-Hsin Hsu, Jui-Hsing Chang.
Methodology: Yu-Mei, Hsueh.
Project administration: Ling-Chu Chien.
Resources: Jui-Hsing Chang.
Software: Guang-Lin Kuo.
Supervision: Yu-Mei, Hsueh, Ling-Chu Chien.
Validation: Ling-Chu Chien.
Visualization: Guang-Lin Kuo.
Writing – original draft: Chuen-Bin Jiang.
Writing – review & editing: Ling-Chu Chien.

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