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Chronic Oral Arsenic Exposure and Its Correlation with Serum S100B Concentration

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Abstract

Arsenic is one of the most important environmental pollutants especially in drinking water. The S100B protein is presented as a sensitive biomarker for assessment of the blood-brain barrier integrity previously. The objective of this study was to determine the impact of chronic arsenic exposure in drinking water and serum S100B correlation. Fifty-four male BALB/c mice were randomly divided into three groups. Group I and II subjects were treated with arsenic trioxide (1 ppm and 10 ppm, respectively), while the rest received normal drinking water. Arsenic concentration in serum and brain was measured by an atomic absorption spectrometer (Varian model 220-Z) conjugated with a graphite furnace atomizer (GTA-110). Also, a serum S100B protein concentration was determined using commercial ELISA kit during different times of exposure. It was observed that body weight gain was significantly lower from the 10th week onwards in arsenic-treated subjects. However, it did not induce any visible clinical signs of toxicity. Measured arsenic level in serum and brain was higher in espoused groups as compared to the control subjects ($p < 0.001$ and $p < 0.0001$, respectively). In addition, serum S100B content was increased over a period of 3 months and had significant differences as compared to the control and 1-ppm group especially after 3 months of exposure in the 10-ppm group ($p < 0.0001$). In conclusion, it could be inferred that long-term arsenic exposure via drinking water leads to brain arsenic accumulation with serum S100B elevated concentration as a probable BBB disruption consequence.

Keywords Arsenic · Blood-brain barrier · S100B · Serum · Heavy metals

Introduction

Since the industrial revolution and the emergence of new ways of life, environmental pollution and its harmful effects on human health have been raised as the most important problem in human societies. Contact with environmental pollution is caused by various factors such as inhaling suspended particles and car smoke, eating foods grown in polluted soils, and drinking contaminated water [1, 2].

Arsenic (As), one of the most important environmental pollutants, is widely distributed in nature, and according to the World Health Organization statistics, it is estimated that more than 200 million people are exposed to high amounts of arsenic that can be dangerous to their health throughout the world [3, 4].

The primary route of exposure to As is through drinking water that has been contaminated by natural geologic sources [5]. Moreover, human activities such as mining, smelting, and refining of certain ores increased the dispersion of arsenic into an environment. A body of articles proved that chronic arsenic exposure is associated with neuropathy [6, 7], skin lesions [8], peripheral vascular disease [9], hypertension, black foot disease [10], and increased risk of cancers [11–14]. Also, recently, the U.S. Environmental Protection Agency (EPA) reduced its acceptable arsenic standard level in public drinking-water sources to 10 ppb [15].

Although both organic and inorganic forms of arsenic exist in nature, humans are mainly exposed to inorganic arsenic through drinking water and occupational resources. In addition, it should be noted that nowadays, inorganic arsenic is

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used as a drug in severe conditions such as promyelocytic leukemia [16].

An association between arsenic ingestion and increased risk of microvascular diseases has been reported previously [17–19]. Moreover, peripheral neuropathy, numbness, tingling of the limbs, and CNS neuronal demyelination with vascular origin have been reported after prolonged exposure to inorganic arsenic [17–19].

The S100B protein belongs to a group of calcium-binding proteins, which is mainly presented in the cytoplasm of glial cells including astrocytes and oligodendrocytes [20, 21]. Measuring plasma concentration of S100B protein is considered as a sensitive biochemical indicator for assessment of neuronal damage including blood-brain barrier disruption or glial cell injury [22]. Recently, it was showed that serum S100B concentrations accurately indicate blood-brain barrier (BBB) dysfunction after traumatic brain injury [23, 24].

In light of these observations, the present study focuses on investigating the possible correlation between inorganic arsenic exposure in drinking water and serum S100B concentration as a putative BBB disruption biomarker.

Material and Methods

Arsenic trioxide (99%, lot no. 02556EN) was purchased from Sigma Aldrich Chemical Company, Inc. (Allentown, PA, USA). All reagents used were of analytical grade and were purchased from Merck (Darmstadt, Germany) unless otherwise mentioned. All glassware and plastic instruments were completely immersed for 24 h in 2 M nitric acid then followed by washing with deionized water. Ultrapure deionized water obtained from a MilliQ water purification system (Millipore, Bedford, USA) was used throughout the experiment.

Animals and Experimental Design

All animal studies were conducted in accordance with guidelines approved by the Institutional Animal Ethics Committee at Isfahan University of Medical Sciences. Fifty-four male mice (20 ± 2 g) were housed in polypropylene cages in an air-conditioned room (temperature 25 ± 4 °C) with a 12-h light/dark cycle and humidity between 60 and 75% with free access to food and water. After 5 days of acclimatization period, they were randomly divided into three groups. Group I and II subjects were treated with arsenic trioxide dissolved in drinking water ad lib (1 ppm and 10 ppm, respectively). The rest of the animals used normal drinking water for the duration of the project to evaluate as a negative control group.

Arsenic Preparation and Sampling

Drinking water containing arsenic was prepared twice a week by dissolving measured quantities of arsenic trioxide in tap water and diluted to a desired concentration. It should be noted that a sufficient volume of NaOH (1 M) was used to solubilize the arsenic trioxide and the final sample was neutralized with HCl (1 M) to an acceptable pH range (7.0–8.0). Total arsenic concentrations in tap water, diet pellets, and diluted samples were checked continuously. In addition, an animal's body weight was checked each week at a fixed time during morning hours.

Six animals of each group were terminated by cervical decapitation at the end of 4, 8, and 12 weeks of exposure, and serum samples were isolated. The brains were taken out immediately, washed in ice-cold saline, and kept at – 20 °C for further analyses [23, 25].

Arsenic Measurement

Total serum and brain arsenic concentration was analyzed using an atomic absorption spectrometer (Varian model 220-Z) conjugated with a graphite furnace atomizer (GTA-110) with a Zeeman background correction. In all determination steps, argon gas with the ultrahigh purity of 99.998% (200 mL min^{-1}) was used as a sheet gas except during the atomization step in which the purge gas flow was interrupted. Throughout the procedure, absorbance values of both peak height and peak area for all standard and samples were measured in triplicate. The performed instrumental parameters and temperature program for the GF-AAS analysis are given in Table 1.

Concentrated nitric acid 65%, hydrogen peroxide 30%, and hydrochloric acid 37% were used for sample preparation and acid digestion. An arsenic stock solution with a concentration of 1 g L^{-1} (Merck Millipore, Darmstadt, Germany) was used to prepare 100 mg L^{-1} standard solution during the measurement procedure. The commercially purchased quality control solutions (certified reference materials) known as CRM (NIES, Japan) were employed for the validation of the proposed method [26].

S100B Assay

Plasma samples' S100B concentration was determined using commercially available enzyme-linked immunosorbent assay kit (Mybiosource, San Diego). All analytical procedures were done according to the manufacturer's instructions. Each sample was assessed in triplicate within an assay, with absorbance measured using a PowerWave plate reader (USA), and the samples' S100B protein concentrations were extrapolated with reference to standard curve.

Table 1 Graphite furnace AAS parameters and temperature program used for the measurement of total arsenic in samples

Instrumental parameters	
Wavelength (nm)	248.3
Slit width (nm)	0.2
Lamp current (mA)	380
Air flow (mL/min)	250
Injection volume (μL)	20
Heating program	Temperature (°C) [ramp time (s), hold time (s)]
Drying 1	110 (1, 20)
Drying 2	154 (5, 30)
Pyrolysis	1150 (15, 10)
Atomization	2100 (0, 5)
Cleaning	2600 (1, 2)

Data Analyses

All statistical evaluation and data processing were carried out by using GraphPad Prism software (La Jolla, CA, USA). Results are expressed as means±SD. To assess the existence of any significant differences between the groups at a given time and to confirm the results of multiple analyses of the groups, non-parametric *F* test (Kruskal-Wallis) was used to compare the groups at each time point. Spearman correlation test was used to determine the relation between measured variables. Values of $p < 0.05$ were defined as statistically significant.

Results

The total number of subjects in each group were 18, 12, and 6 at the first, second, and third months, respectively. On the whole, oral exposure to arsenic even at 10-ppm dose in drinking water for a period of 3 months did not induce visible clinical signs of toxicity or other physical changes (depression, paralysis, etc.) except significant change in weight gain.

Comparison of the subjects' mean body weight at the start time of the test between the groups was not statistically significant (*p* value 0.182 and *F* 1.756). The non-parametric correlation test done to evaluate time-dependent trend for weight gain among different groups proved that there was a positive and significant correlation between time and weight gain in each group (*r* 0.989 and *p* value < 0.0001). As inferred from Fig. 1, there was a steady increase in the body weight of subjects in all groups until the 10th week, but the net growth rate was almost 0 in both arsenic-treated groups from the 11th week onwards. However, the statistically significant difference was only observed between control and 10-ppm-treated subjects at the endpoint of the study (Mann Whitney test *p* value 0.04).

Analyses of the diets showed that the actual metal content was less than 10% of administered values. Statistical analysis of any meaningful differences between groups in the first and third months was examined by two-way *F* test followed by Tukey's multiple comparison test (Fig. 2).

It was observed that the amount of measured arsenic in the serum of treated mice with 10 ppm arsenic trioxide after 3 months of exposure was significantly higher than that in the first month of exposure ($F = 298$, p value < 0.0001). However, there was no significant difference between the first and third months of control or 1-ppm arsenic-exposed groups in serum arsenic level. Comparison between groups at each time interval shows that measured serum arsenic level was higher in the exposed groups of 1 and 10 ppm versus that in the control group ($p < 0.001$ and $p < 0.0001$, respectively).

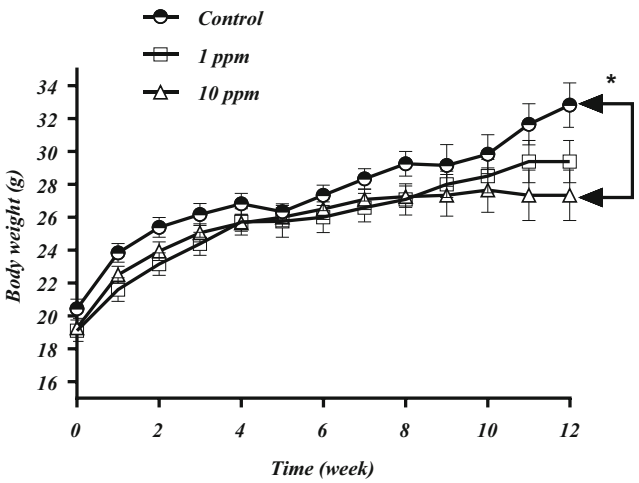

Fig. 1 Arsenic trioxide was given in drinking water as 1 ppm and 10 ppm for 12 weeks. Control group subjects were given tap water ad lib. The body weights were taken at 1-week intervals. All groups' mean body weight showed positive correlation until 10 weeks of observation. Meanwhile, recorded data showed that, after the 11th week of treatment with arsenic, mean body weight in 10-ppm arsenic-treated subjects was significantly lower as compared with that in the control group. Data are presented as mean ± SEM. *p value < 0.05

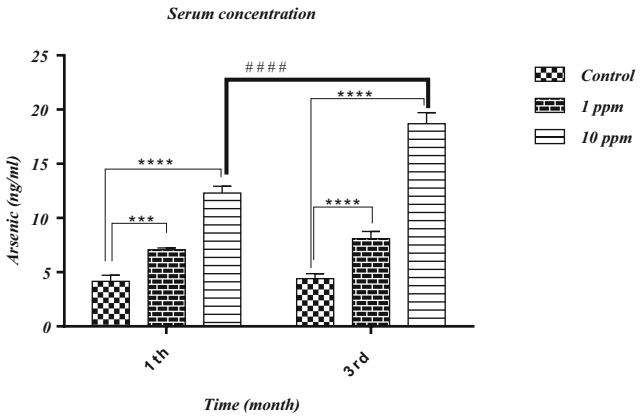

Fig. 2 Serum arsenic concentrations (ng mL^{-1}) in the three groups exposed to arsenic trioxide via drinking water (1 and 10 ppm). Data were presented as mean ± SD. Statistically significant differences were examined by two-way ANOVA followed by Tukey's multiple comparison test. The asterisk indicates significant variation as compared to that of control group at the same period of observation. The number sign shows significant variation between the same groups at different time exposures. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$; $^{\#\#\#\#}p < 0.0001$

In comparing the amount of arsenic in the brain of a group treated with 10 ppm arsenic, a significant difference with the control group was shown in both measured times. However, this difference was not observed in the 1-ppm group as compared to the control group in the first month (Fig. 3).

Between-groups variation analysis at each time interval shows that measured serum arsenic level was higher in the exposed groups of 1 and 10 ppm versus that in the control group ($p < 0.001$ and $p < 0.0001$, respectively). Meanwhile, the same test among 1- and 10-ppm groups showed more significant variation after 12 weeks exposure versus 4 weeks ($p < 0.0001$ vs. $p < 0.05$, respectively).

The within-group analysis did not show a significant difference between the control or 1-ppm group subjects in the first month versus the third month of the study, although this statistical variation was clearly observed in 10-ppm arsenic group toward increasing the value based on the time of exposure.

In comparison of all groups, the brain arsenic content was higher than the measured values in serum regardless of the time of measurement. In the analyses conducted to examine the existence of any statistically significant differences between these concentrations, it was observed that only the control group's p values had a significant variation in the first month of the study duration. Meanwhile, the comparison of the measured values at the end of the third month indicated that there was no significant difference in the control group. In contrast, comparing the treated group with 1 or 10 ppm arsenic concentrations has shown a sharp increase and significant difference after 3 months exposure from the starting day especially in 10-ppm-treated subjects (Table 2).

As shown in Fig. 4, comparison of serum S100B changes showed that there were no significant differences between control or 1-ppm group by increasing time exposure. However, in association with the 10-ppm group, serum S100B protein was increased over a period of 3 months and had significant differences as compared to the control and 1-ppm groups.

Total correlation between arsenic concentration in serum, brain, and released S100B was provided in Fig. 5. It was observed that a positive correlation exists among serum S100B and brain arsenic content especially in 10-ppm-treated subjects ($r = 0.96$, p value < 0.001).

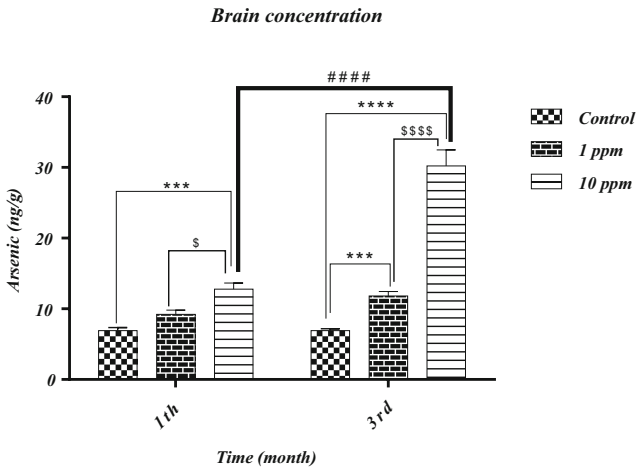

Fig. 3 Arsenic concentrations (ng g^{-1}) in the brain between control and arsenic trioxide-treated groups (1 and 10 ppm) via drinking water. Data were presented as mean ± SD. Statistically significant differences were examined by two-way ANOVA followed by Tukey's multiple comparison test. The asterisk indicates significant variation as compared to that of the control group at the same period of observation. The number sign shows significant variation between the same groups at different time exposures. $^{***}p < 0.001$; $^{****}p < 0.0001$; $^{\$}p < 0.05$; $^{\$\$\$\$}p < 0.0001$; $^{\#\#\#\#}p < 0.0001$

Discussion

Arsenic, one of the most natural toxic agents, is a water-borne contaminant which endangers the health of millions of people around the world. Trivalent arsenite (AsIII) and pentavalent arsenate (As V) are the two major inorganic arsenic contaminants in water [27]. Meanwhile, throughout the cells, cytosol arsenate is usually reduced to arsenite [28]. In addition, the most potent toxic form of arsenic is arsenic trioxide which has a faster absorption than pentavalent arsenic in gastrointestinal epithelium cells.

In our study, it was observed that arsenic exposure in drinking water for 3 months did not produce any visible clinical signs; however, treatment with 10 ppm arsenic for 12 weeks induced a significantly lower body weight as compared to control group subjects. In accordance with our observation,

Table 2 Arsenic concentration (ppb) in brain and serum of each group subject after 4 and 12 weeks exposure to arsenic trioxide in drinking water

Groups	1st month		p value*	Mean Diff.	3rd month		p value	Mean Diff.
	Serum	Brain			Serum	Brain		
Control	4.15 ± 0.56	6.90 ± 0.46	0.031	2.75	4.40 ± 0.45	6.93 ± 0.25	0.062	2.53
1 ppm	7.07 ± 0.18	9.20 ± 0.61	0.182	2.14	8.10 ± 0.66	11.80 ± 0.64	0.001	3.70
10 ppm	12.29 ± 0.64	12.79 ± 0.85	0.998	0.49	18.70 ± 1.01	30.21 ± 2.28	0.000	11.51

Values were presented as mean ± SD. Statistically significant differences were examined by two-way F test followed by Tukey's multiple comparison test. *p value lower than 0.05

Nandi and colleagues observed that the mean body weights of oral arsenic-treated rats were significantly lower from the 10th week onwards and the rats had a comparatively poor body weight gain during the time of exposure [29]. Also, the same decreasing pattern relative to that in the control group in net body weight and net body weight gain was shown in rats treated with 10 mg kg^{-1} arsenic every day [26]. The observed weight reduction in exposed animals could be due to a reduction in food intake, disruption in the absorption of nutrients from the gastrointestinal tract, impaired cellular metabolism, and decreased efficiency of food energy conversion into body weight gain [30].

In our study, although the exposed dose of arsenic was low, it has been observed that long-term exposure through drinking water leads to arsenic accumulation in serum. Rowland and colleagues observed that after sodium arsenate treatment in rats, arsenic is rapidly absorbed and accumulated in the blood and to a lesser extent in the liver, kidney, lungs, and spleen [31]. Also, using radioactive arsenic proved that treatment with 0.5 mg of arsenic per kilogram of body weight for 9 days in mice leads to serum arsenic level remaining in a stable

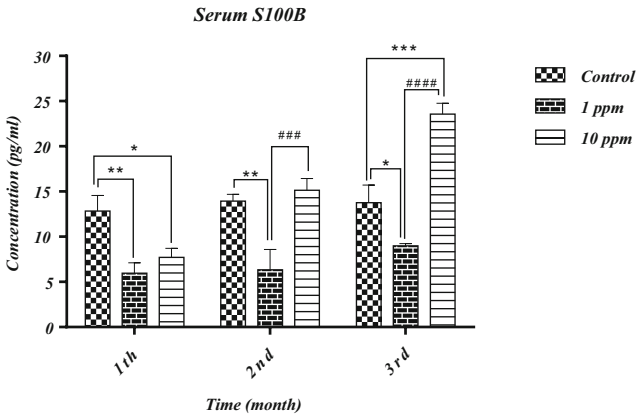

Fig. 4 Measured serum S100B concentrations (pg mL^{-1}) in the three groups exposed to arsenic trioxide via drinking water (1 and 10 ppm). Data were presented as mean ± SD. Statistically significant differences were examined by two-way ANOVA followed by Tukey's multiple comparison test. The asterisk indicates significant variation as compared to that of control group at the same period of observation. The number sign shows significant variation between 1- and 10-ppm-treated groups. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ###$p < 0.001$; ####$p < 0.0001$

concentration [32]. Arsenic can easily cross the cell membranes through specific channels because of the arsenate and arsenite chemical structure similar to the required nutrients. Various transporters, including glucose transporters (GLUT and SGLT), organic anion transporting polypeptides (OATPs), aquaporins (AQPs), and phosphate transporters (NaPi and PiT), participate in the absorption of As (V) and As (III) [33].

It was observed that the brain arsenic content was higher than measured serum values in all groups regardless of the time of measurement. Comparing treated group with control subjects has shown that brain arsenic content had a sharp increase after 3 months exposure from the starting day, especially in the 10-ppm group. At physiological pH, arsenite converts to As oH_3 inert form, which resembles organic molecules such as glycerol [34]. As mentioned above, integral membrane channel proteins such as aquaporins are responsible to flux water and small selected molecules via cellular barriers such as BBB. The specific subfamily of AQPs named aquaglyceroporins (AQP3, AQP7, AQP9, and AQP10) transports larger molecules such as glycerol. It was sown that this subfamily is responsible for transporting arsenite in mammalians [35].

Recently, it was shown that another membrane protein family including GLUT1 and GLUT4 also promotes uptake of both arsenite and monomethylarsenite (MMA (III)) [29, 34, 36]. Since GLUT1 is the main glucose transporter and is more widely distributed than AQP7 and AQP9, it may assume being the major arsenic transporter into the brain and might contribute to arsenic-related neurotoxicity [37].

Serum S100B comparison between 1-ppm and control groups showed that by increasing the time of exposure there was no significant change in the measured value; however, in 10-ppm treatment, total serum S100B content was increased over a period of 3 months and had significant differences as compared to the control and 1-ppm groups especially after 3 months of exposure. In accordance with previous observations, it could be inferred that 3 months exposure to 10 ppm arsenic in drinking water (1000× of the acceptable range for human exposure) increased the S100B serum content; this elevation may be due to BBB disruption because of excessive lipid peroxidation [38, 39].

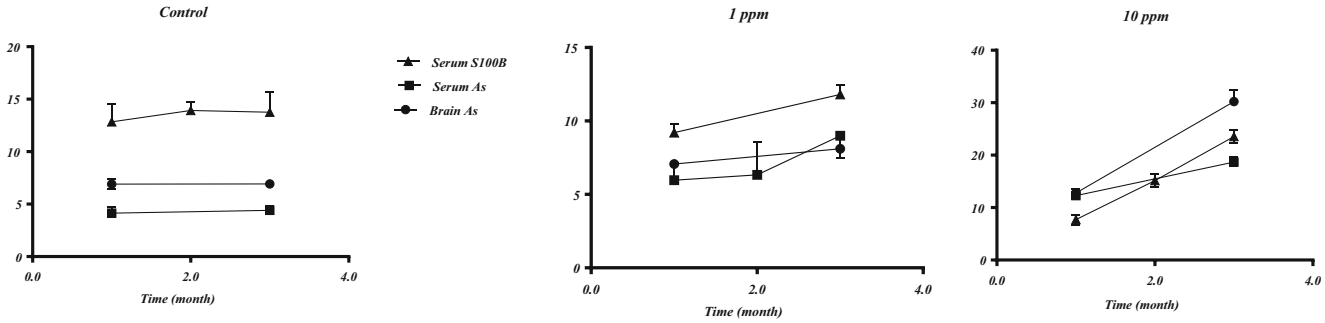

Fig. 5 Correlation between measured serum S100B concentrations (pg mL^{-1}) and arsenic in serum/brain in the subjects exposed to arsenic trioxide via drinking water (1 and 10 ppm). Data were presented as mean ± SD. Comparison was done with Spearman correlation test

The S100B protein (molecular weight 10 kDa) belongs to S100 family, a group of calcium-binding proteins, which is mainly presented in the cytoplasm of the choroid plexus and glia (astrocyte and oligodendrocytes) and Schwann cells [22]. Measuring serum concentration of S100B protein is considered as a sensitive biochemical indicator for assessment of neuronal damage including blood-brain barrier disruption or glia cell injury. Recently, it was shown that serum S100B concentrations accurately indicate BBB dysfunction in comparison with other biomarkers such as albumin and prealbumin [40, 41]. Over the past decade, numerous studies have reported a positive correlation between S100B levels in the blood due to brain stroke, intracerebral hemorrhage, or in major depression [37, 42]. It has suggested that S100B has leaked through the disrupted BBB because of glial cell damage after middle cerebral artery occlusion (MCAO)-induced model [43]. In addition, it was shown that release of S100 protein in peripheral blood was raised after brain ischemic damage [44–46]. Briefly, S100B protein was introduced as a peripheral biomarker in forecasting long-term outcomes including BBB disruption or even neurological damages [47–49].

To evaluate the extent of brain damage due to arsenic exposure, it was observed that orally administered arsenic with various concentrations (0.05, 0.1, 0.3, and 3 ppm) increased the markers of lipid peroxidation and reduced the activity of superoxide dismutase and glutathione reeducates in relation to the excess free radicals production in rat brain [50, 51]. In our study, it was expected that serum S100B concentrations show two different releasing manners. First of all, it could be quickly raised due to BBB vascular endothelial damage because of arsenic's proven characteristics [18] or slowly increased because of the time-consuming process of arsenic entrance through the mentioned pathways, and accumulation and induction of glial cell damage due to excess lipid peroxidation in brain as it was shown previously [52]. In short, to some extent, the second hypothesis came true in this observation.

In conclusion, it could be inferred that long-term arsenic exposure via drinking water leads to arsenic accumulation in brain with elevated serum S100B concentration as a probable BBB disruption consequence, although further investigations would be necessary for longer arsenic exposure to clarify the exact correlation between S100B release and BBB disruption with Evans blue dye and the brain oxidative damage markers.

Compliance with Ethical Standards

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

References

1. Wei B, Yu J, Wang J, Li H, Yang L, Kong C (2017) Trace metals in the urine and hair of a population in an endemic arsenism area. Biol Trace Elem Res:1–8
2. Nriagu JO (1996) A history of global metal pollution. Science 272(5259):223–220
3. No WFS (2000) Arsenic in drinking water
4. Chakraborti D, Rahman MM, Ahamed S, Dutta RN, Pati S, Mukherjee SC (2016) Arsenic groundwater contamination and its health effects in Patna district (capital of Bihar) in the middle Ganga plain, India. Chemosphere 152:520–529
5. Kozul CD, Hampton TH, Davey JC, Gosse JA, Nomikos AP, Eisenhauer PL, Weiss DJ, Thorpe JE, Ihnat MA, Hamilton JW (2009) Chronic exposure to arsenic in the drinking water alters the expression of immune response genes in mouse lung. Environ Health Perspect 117(7):1108–1115
6. Chandravanshi LP, Gupta R, Shukla RK (2018) Developmental neurotoxicity of arsenic: involvement of oxidative stress and mitochondrial functions. Biol Trace Elem Res:1–14
7. Trivedi S, Pandit A, Ganguly G, Das SK (2017) Epidemiology of peripheral neuropathy: an Indian perspective. Ann Indian Acad Neurol 20(3):173–184
8. Niedzwiecki MM, Liu X, Zhu H, Hall MN, Slavkovich V, Ilievski V, Levy D, Siddique AB, Kibriya MG, Parvez F (2018) Serum homocysteine, arsenic methylation, and arsenic-induced skin lesion incidence in Bangladesh: a one-carbon metabolism candidate gene study. Environ Int 113:133–142
9. Newman JD, Navas-Acien A, Kuo C-C, Guallar E, Howard BV, Fabsitz RR, Devereux RB, Umans JG, Francesconi KA, Goessler W (2016) Peripheral arterial disease and its association with arsenic exposure and metabolism in the Strong Heart Study. Am J Epidemiol:1–12
10. Barchowsky A, States JC (2015) Arsenic-induced cardiovascular disease. Arsenic: exposure sources, health risks, and mechanisms of toxicity:453

11. Cardoso AP, Al-Eryani L (2018) Arsenic-induced carcinogenesis: the impact of miRNA dysregulation. Toxicol Sci
12. Fry RC (2018) Abstract IA16: Identifying an epigenetic basis for arsenic-associated bladder cancer in a population in Chihuahua Mexico. AACR
13. Wang W, Cheng S, Zhang D (2014) Association of inorganic arsenic exposure with liver cancer mortality: a meta-analysis. Environ Res 135:120–125
14. Smith AH, Hopenhayn-Rich C, Bates MN, Goeden HM, Hertz-Picciotto I, Duggan HM, Wood R, Kosnett MJ, Smith MT (1992) Cancer risks from arsenic in drinking water. Environ Health Perspect 97:259–267
15. Petty MA, Berryman GE, Jones GH (2018) Arsenic remediation of drinking water using limestone
16. Kayser S, Krzykalla J, Elliott M, Norsworthy K, Gonzales P, Hills R, Baer M, Ráčil Z, Mayer J, Novak J (2017) Characteristics and outcome of patients with therapy-related acute promyelocytic leukemia front-line treated with or without arsenic trioxide. Leukemia 31(11):2347–2354
17. Song X, Li Y, Liu J, Ji X, Zhao L, Wei Y (2017) Changes in serum adiponectin in mice chronically exposed to inorganic arsenic in drinking water. Biol Trace Elem Res 179(1):140–147
18. Chaudhuri AN, Basu S, Chattopadhyay S, Gupta SD (1999) Effect of high arsenic content in drinking water on rat brain
19. Gharibzadeh S, Hoseini SS (2008) Arsenic exposure may be a risk factor for Alzheimer's disease. J Neuropsychiatr Clin Neurosci 20(4):501–501
20. Vahidnia A, Van der Voet G, De Wolff F (2007) Arsenic neurotoxicity—a review. Hum Exp Toxicol 26(10):823–832
21. Aliomrani M, Sahraian MA, Shirkhanloo H, Sharifzadeh M, Khoshayand MR, Ghahremani MH (2016) Blood concentrations of cadmium and lead in multiple sclerosis patients from Iran. Iran J Pharm Res: IJPR 15(4):825–833
22. Korfias S, Stranjalis G, Papadimitriou A, Psachoulia C, Daskalakis G, Antsaklis A, Sakas D (2006) Serum S-100B protein as a biochemical marker of brain injury: a review of current concepts. Curr Med Chem 13(30):3719–3731
23. Gahlot G, Soni Y, Joshi G, Saxena R (2017) Clinical significance of serum biomarker S100B to predict outcome after traumatic brain injury. Indian J Mednodent Allied Sci 5(1):24–29
24. Di Pietro V, Amorini AM, Lazzarino G, Yakoub KM, D'Urso S, Lazzarino G, Belli A (2015) S100B and glial fibrillary acidic protein as indexes to monitor damage severity in an in vitro model of traumatic brain injury. Neurochem Res 40(5):991–999
25. Barateiro A, Afonso V, Santos G, Cerqueira JJ, Brites D, van Horssen J, Fernandes A (2016) S100B as a potential biomarker and therapeutic target in multiple sclerosis. Mol Neurobiol 53(6): 3976–3991
26. Nandi D, Patra R, Swarup D (2006) Oxidative stress indices and plasma biochemical parameters during oral exposure to arsenic in rats. Food Chem Toxicol 44(9):1579–1584
27. Aliomrani M, Sahraian MA, Shirkhanloo H, Sharifzadeh M, Khoshayand MR, Ghahremani MH (2017) Correlation between heavy metal exposure and GSTM1 polymorphism in Iranian multiple sclerosis patients. Neurol Sci 38(7):1271–1278
28. Mukhopadhyay R, Rosen BP, Phung LT, Silver S (2002) Microbial arsenic: from geocycles to genes and enzymes. FEMS Microbiol Rev 26(3):311–325
29. Hamdi M, Sanchez MA, Beene LC, Liu Q, Landfear SM, Rosen BP, Liu Z (2009) Arsenic transport by zebrafish aquaglyceroporins. BMC Mol Biol 10(1):104
30. Holson J, Stump D, Clevidence K, Knapp J, Farr C (2000) Evaluation of the prenatal developmental toxicity of orally administered arsenic trioxide in rats. Food Chem Toxicol 38(5):459–466
31. Mahaffey KR, Fowler BA (1977) Effects of concurrent administration of lead, cadmium, and arsenic in the rat. Environ Health Perspect 19:165–171
32. Rowland IR, Davies MJ (1982) Reduction and methylation of sodium arsenate in the rat. J Appl Toxicol 2(6):294–299
33. Hughes MF, Kenyon EM, Edwards BC, Mitchell CT, Del Razo LM, Thomas DJ (2003) Accumulation and metabolism of arsenic in mice after repeated oral administration of arsenate. Toxicol Appl Pharmacol 191(3):202–210
34. Calatayud M, Barrios JA, Vélez D, Devesa V (2012) In vitro study of transporters involved in intestinal absorption of inorganic arsenic. Chem Res Toxicol 25(2):446–453
35. Ramírez-Solís A, Mukopadhyay R, Rosen BP, Stemmler TL (2004) Experimental and theoretical characterization of arsenite in water: insights into the coordination environment of As− O. Inorg Chem 43(9):2954–2959
36. Yang H-C, Fu H-L, Lin Y-F, Rosen BP (2012) Chapter twelve - pathways of arsenic uptake and efflux. In: Argüello JM, Lutsenko S (eds) Current topics in membranes, vol 69. Academic Press, pp 325–358. doi:https://doi.org/10.1016/B978-0-12-394390-3.00012-4
37. Liu Z, Sanchez MA, Jiang X, Boles E, Landfear SM, Rosen BP (2006) Mammalian glucose permease GLUT1 facilitates transport of arsenic trioxide and methylarsonous acid. Biochem Biophys Res Commun 351(2):424–430
38. Prakash C, Soni M, Kumar V (2016) Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: a review. J Appl Toxicol 36(2):179–188
39. Singh V, Kushwaha S, Gera R, Ansari JA, Mishra J, Dewangan J, Patnaik S, Ghosh D (2018) Sneaky entry of IFNγ through arsenic-induced leaky blood–brain barrier reduces CD200 expression by microglial pro-inflammatory cytokine. Molecular Neurobiology: 1–12
40. Falcone T, Miniard A, Anand A (2018) F155. Blood brain barrier integrity biomarkers of suicide in adolescents. Biol Psychiatry 83(9):S298
41. Loftis JM, Valerio J, Taylor J, Huang E, Hudson R, Taylor-Young P, Chang M, Ho SB, Dieperink E, Miranda JL (2018) S100B and inflammatory cytokine levels in blood as potential markers of blood–brain barrier damage and psychiatric impairment in comorbid hepatitis C viral infection and alcohol use disorder. Alcoholism: Clinical and Experimental Research
42. Rosen BP, Liu Z (2009) Transport pathways for arsenic and selenium: a minireview. Environ Int 35(3):512–515
43. Kleindienst A, Schmidt C, Parsch H, Emtmann I, Xu Y, Buchfelder M (2010) The passage of S100B from brain to blood is not specifically related to the blood-brain barrier integrity. Cardiovasc Psychiatry Neurol 2010:1–8
44. Hårdemark H-G, Ericsson N, Kotwica Z, Rundström G, Mendel-Hartvig I, Olsson Y, Påhlman S, Persson L (1989) S-100 protein and neuron-specific enolase in CSF after experimental traumatic or focal ischemic brain damage. J Neurosurg 71(5):727–731
45. Matsui T, Mori T, Tateishi N, Kagamiishi Y, Satoh S, Katsube N, Morikawa E, Morimoto T, Ikuta F, Asano T (2002) Astrocytic activation and delayed infarct expansion after permanent focal ischemia in rats. Part I: enhanced astrocytic synthesis of S-100β in the periinfarct area precedes delayed infarct expansion. J Cereb Blood Flow Metab 22(6):711–722
46. Kanner AA, Marchi N, Fazio V, Mayberg MR, Koltz MT, Siomin V, Stevens GH, Masaryk T, Ayumar B, Vogelbaum MA (2003) Serum S100β. Cancer 97(11):2806–2813
47. Woertgen C, Rothoerl RD, Brawanski A (2001) Neuron-specific enolase serum levels after controlled cortical impact injury in the rat. J Neurotrauma 18(5):569–573
48. Missler U, Wiesmann M, Friedrich C, Kaps M (1997) S-100 protein and neuron-specific enolase concentrations in blood as indicators of

infarction volume and prognosis in acute ischemic stroke. Stroke 28(10):1956–1960

49. Wunderlich MT, Ebert AD, Kratz T, Goertler M, Jost S, Herrmann M (1999) Early neurobehavioral outcome after stroke is related to release of neurobiochemical markers of brain damage. Stroke 30(6): 1190–1195
50. Tanaka Y, Koizumi C, Marumo T, Omura T, Yoshida S (2007) Serum S100B indicates brain edema formation and predicts long-term neurological outcomes in rat transient middle cerebral artery occlusion model. Brain Res 1137:140–145
51. Steiner J, Schiltz K, Walter M, Wunderlich MT, Keilhoff G, Brisch R, Bielau H, Bernstein H-G, Bogerts B, Schroeter ML (2010) S100B serum levels are closely correlated with body mass index: an important caveat in neuropsychiatric research. Psychoneuroendocrinology 35(2):321–324
52. Kim J-H, Byun H-M, Chung E-C, Chung H-Y, Bae O-N (2013) Loss of integrity: impairment of the blood-brain barrier in heavy metal-associated ischemic stroke. Toxicol Res 29(3):157–164