OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2023;8(4):533-538 *Online Türk Sağlık Bilimleri Dergisi 2023;8(4):533-538*

Determination of Mercury, Cadmium, Arsenic Levels and Their Relationship with Seizure Duration in Children with Simple Febrile Seizures

Basit Febril Nöbetli Çocuklarda Civa, Kadmiyum, Arsenik Düzeyleri ve Nöbet Süresi ile İlişkilerinin Belirlenmesi

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ABSTRACT

Objective: Heavy metals may cause neuronal damage by inducing oxidative stress. This study aims to investigate the levels of mercury, cadmium, and arsenic in children with febrile seizures and their correlation with seizure duration.

Materials and Methods: The study was conducted on 40 children who experienced simple febrile seizures and 30 children who had a fever but did not experience seizures. The study analyzed complete blood count, serum high-sensitive C-reactive protein, albumin, whole blood mercury, cadmium, and arsenic levels. The analysis was conducted six hours after the seizure for those who experienced seizures and six hours after the onset of fever for those who did not experience seizures.

Results: Our study found that the patient group had significantly higher levels of arsenic in their blood compared to the control group. At the same time, there was no significant difference in the levels of mercury and cadmium. However, we could not establish any relationship between the seizure duration and the heavy metals levels.

Conclusions: While mercury and cadmium levels are normal in children with simple febrile seizures, arsenic levels are high. However, the levels of all three heavy metals have no relationship with the duration of seizures.

Keywords: Arsenic, cadmium, mercury, simple febrile seizure

ÖZ

Amaç: Ağır metallerin oksidatif stresi tetikleyerek nöronal hasara katkıda bulunmaları muhtemeldir. Bu çalışmanın amacı, basit febril nöbet geçiren çocuklarda civa, kadmiyum ve arsenik düzeylerinin saptanarak nöbet süresi ile ilişkilerinin belirlenmesidir.

Materyal ve Metot: 40 basit febril nöbetli çocukta nöbet sonrası altıncı saatte, 30 ateşli ancak nöbeti olmayan çocukta ise ateş şikayetinin başlangıcından altı saat sonra tam kan sayımı, serum high sensitive c reaktif protein, albümin, tam kan civa, kadmiyum ve arsenik düzeyleri çalışılmıştır.

Bulgular: Çalışmamızda ağır metallerden civa ve kadmiyum kan düzeylerinde kontrol grubuna göre anlamlı fark bulunmazken, arsenik düzeyleri hasta grubunda anlamlı şekilde yüksek bulunmuştur. Ağır metallerin nöbet süresi ile ilişkisi saptanmamıştır.

Sonuç: Basit febril nöbetli çocuklarda civa ve kadmiyum düzeyleri normal iken arsenik düzeyleri yüksektir. Ancak her üç ağır metal düzeyinin de nöbet süresi ile ilişkisi bulunmamaktadır.

Anahtar Kelimeler: Arsenik, basit febril nöbet, civa, kadmiyum

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Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 07/11/2023
Kabul Tarihi/ Accepted: 19/11/2023
Online Yayın Tarihi/ Published: 18/12/2023

Atıf / Cited: Elmas B. Determination of Mercury, Cadmium, Arsenic Levels and Their Relationship with Seizure Duration in Children with Simple Febrile Seizures. *Online Türk Sağlık Bilimleri Dergisi* 2023;8(4):533-538. doi: 10.26453/otjhs.1387567

INTRODUCTION

A febrile seizure is the most common type of seizure in children.[1] It is classified into two categories - simple and complex, based on their clinical characteristics. Simple febrile seizures are generalized seizures that last less than 15 minutes and do not reoccur within 24 hours. On the other hand, complex febrile seizures are focal seizures that last longer than 15 minutes or reoccur more than once within the first 24 hours.[2]

Complex febrile seizures in early childhood are known to have a high risk of recurrence and increase the likelihood of developing afebrile seizures in the future.[3] Although considered benign during early childhood, it has been reported that the risk of developing epilepsy in the future is slightly higher than the average population, even in cases of simple febrile seizures.[1]

Seizures can cause damage to neurons through a critical mechanism. When a seizure occurs, excessive amounts of calcium enter the cell through N methyl D aspartate and voltage-dependent channels. This leads to high levels of calcium inside the cell, which triggers various biochemical processes and stimulates the production of reactive oxygen molecules (ROS).[5]

Oxidative stress, which occurs with the increase in reactive oxygen molecules, leads to deterioration in cellular communication and some other cellular functions.[6] The degree of oxidative stress is related to the body's antioxidant capacity.[7] Heavy metals are important factors that trigger oxidative stress and lead to a decrease in antioxidant capacity.[8] These heavy metals, which are likely to be exposed to environmentally in children, trigger oxidative stress by reducing antioxidant capacity.[9-12]

Febrile seizures in patients exposed to arsenic, mercury, or cadmium are likely to trigger oxidative stress earlier and more severely due to low levels of antioxidants. This study aims to determine the levels of heavy metals in children with simple febrile seizures and their correlation with the duration of the seizures.

MATERIALS AND METHODS

Ethical Committee Approval: The study was conducted in the Pediatric Emergency Unit of Sakarya Training and Research Hospital between 01.08.2017 and 01.08.2018, and approval was received from the Sakarya University Faculty of Medicine Ethics Committee (Date: 29.05.2017, decision no: 16214662/050.01.04/48). The study was carried out in accordance with the International WHO Declaration of Helsinki.

Study Population: In our study, 40 patients aged between 8 and 59 months who were admitted to the Pediatric Emergency Department and diagnosed with simple febrile seizures were compared with 30 controls of similar age who had fever but did not have febrile seizures.

The study recorded demographic data of the patients, such as their exposure to cigarette smoke in their living environment, the way their house was heated, drinking water sources, weekly fish consumption, and shift duration information.

Collection of Samples: The patient group had their complete blood count (CBC), serum high-sensitive C-reactive protein (hs-CRP), albumin, whole blood mercury, cadmium, and arsenic levels studied six hours after the seizure, while the control group had these measurements taken six hours after the onset of fever complaint. Since it was thought that consent from the families could not be obtained during admission to the hospital, the samples were taken at the sixth hour.

Analysis Methods: To analyze arsenic, mercury, and cadmium levels in whole blood, blood samples were collected from the subjects using 10mm EDTA-containing trace element tubes from BD Vacutainer (New Jersey, USA). An automated complete blood count device (Celldyn 3400, Abbott Diagnostics, USA) was used to measure the WBC count. At the same time, serum hs-CRP was analyzed using a BN II analyzer from Siemens Healthcare Diagnostics Products GmbH (Marburg, Germany). Serum albumin was studied using a fully automatic autoanalyzer (AU 5800, Beckman Coulter, Tokyo, Japan). Whole blood arsenic, mercury, and cadmium levels were analyzed using the Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method (Agilent 7700 series, Tokyo, Japan).

Statistical Analysis: The statistical analysis was carried out using the SPSS software (IBM SPSS Statistics, Version 22.0 Armonk, NY: IBM Corp.). Categorical variables are presented as numbers (n) and percentages (%). The Student's t-test or Mann-Whitney U test was used for comparison between two groups, whereas ANOVA was used for more than two groups when the data showed normal distribution. For non-normal distribution data, the Kruskal-Wallis test was used to compare more than two groups. The Chi-Square test was used for comparison between groups consisting of categorical variables. The Spearman linear correlation coefficient was calculated to determine the relationship between numerical variables. A significance level of $p< 0.050$ was considered.

RESULTS

Our study did not find any difference in heavy metal exposure risk between the patient and control groups based on their drinking water source, weekly fish

consumption, heating style of the house, and smoking status at home. The patient and control groups also did not show any significant differences in WBC, hs-CRP, albumin, mercury, and cadmium levels. However, we observed significantly higher arsenic levels in the patient group (Table 1).

In the study, it was observed that there was no difference in the blood mercury levels of people who consumed fish less than once a week and those who consumed fish 1-2 times a week (0.27 [0.11-0.77] µg/L, 0.27 [0.11-0, 75] µg/L, 0.34 [0.16-0.73] µg/L, respectively) (p = 0.689) (Figure 1).

Blood cadmium levels were measured in individuals who were exposed to cigarette smoke at home (0.33 [0.13-1.12] µg/L) as well as those who were not (0.23 [0.11-2.26] µg/L). There was no significant difference in blood cadmium levels between those who were exposed to stove smoke (0.24 [0.11-1.11] µg/L) and those who were not (0.24 [0.11-2.26] µg/L) (p=0.08, p=0.760, respectively) (Figure 2).

Table 1. Comparison of demographic, environmental, acute phase reactants, and heavy metal levels in patients and controls.

Variable		Febrile Seizures (n=40)	Control (n=30)	p-value
Age (months), Median (Min-Max)		23.50 (8-78)	29.50 (4-71	0.850[a]
Genders, n (Female/Male)		16/24	12/18	1[b]
Smoking at home, n (%)	Yes	18 (45)	10 (33)	0.320[b]
	No	22 (55)	20 (77)	
The shape of the house heating, n (%)	Stove (solid fuel	19 (48)	12 (40)	0.530[b]
	Heating (natural gas)	21 (52)	18 (60)	
Drinking water supply, n (%)	Company's water	14 (35)	16 (54)	0.260[b]
	Pet bottle-demijohn water	20 (50)	12 (40)	
	Natural spring water	6 (15)	2 (6)	
Fish consumption, n (%)	No	13 (33)	16 (53)	0.110[b]
	Once a week	22 (55)	9 (30)	
	Two or more a week	5 (12)	5 (17)	
WBC (mm^3), Median (Min-Max)		9445(4040-32000)	8600 (3500-16800)	0.530[a]
hs-CRP (mg/L), Median (Min-Max)		1.07 (0.10-3.48)	0,55 (0.32-2.72)	0.920[a]
Albumin (g/dL), Median (Min-Max)		4.10 (3.40-4.80)	4,21 (3.80-4.50)	0.400[a]
Mercury(mg/L), Median (Min-Max)		0.30 (0.11-0.75)	0.23 (0.11-0.77)	0.400[a]
Cadmium (mg/L), Median (Min-Max)		0.24 (0.11-1.20)	0.21 (0.11-2.26)	0.450[a]
Arsenic(mg/L), Median (Min-Max)		1.17 (0.13-6.55)	0.57 (0.16-2.67)	**0.020[a]**

WBC: White blood cell; hs-CRP: High sensitivity c-reactive protein; The results shown as median (minimum-maximum) or frequency; [a]: Mann Whitney U; [b]: Chi-square; Mercury, cadmium and arsenic normal range: 0-10mg/L, 0-4.9mg/L, 0-12mg/L, respectively; p-value<0.05 was considered significant.

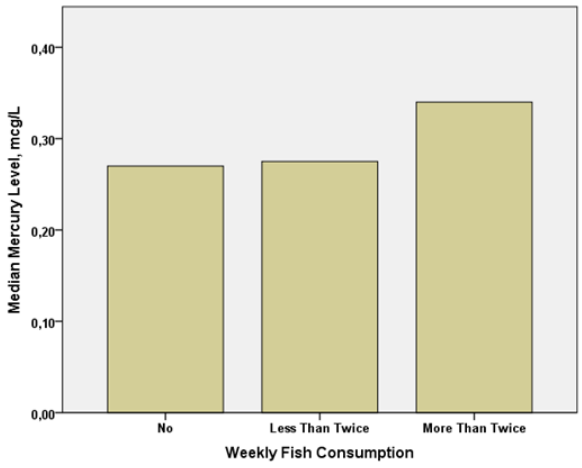

Figure 1. Blood mercury levels according to weekly fish consumption.

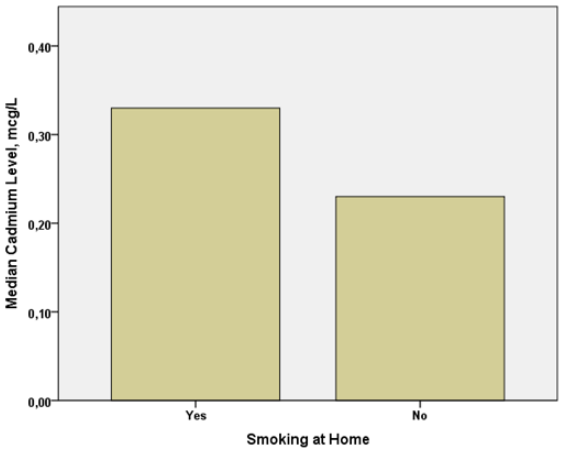

Figure 2. Blood cadmium levels according to exposure to smoking.

Blood arsenic levels were measured in drinking water from city tap water (1.02[0.13-3.72] µg/L), demijohn or plastic bottle (0.79[0.15-6.55] µg/L) and natural spring water (1.02[0.18-2.72] µg/L). No significant differences were found between the sources of water (p=0.920) (Figure 3).

Our study found that 32 out of 40 patients (80%) with simple febrile seizures had a seizure duration of less than 5 minutes, while 8 patients (20%) had a seizure duration longer than 6 minutes. However, we did not find any significant correlation between seizure durations and levels of mercury, cadmium, and arsenic, as shown in Table 2.

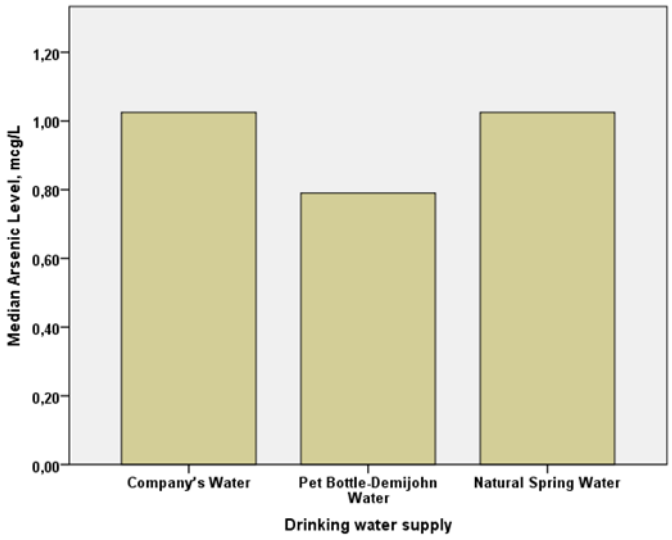

Figure 3. Blood arsenic levels according to drinking water.

Table 2. Correlation analysis between seizure durations and heavy metal levels.

Parameters	Seizure duration	
	rho	p-value
Mercury	-0.072	0.692
Cadmium	-0.016	0.928
Arsenic	0.010	0.957

Spearman correlation analysis was performed.

DISCUSSION AND CONCLUSION

Our study found that although there was no noticeable variance in mercury and cadmium blood levels compared to the control group, patients showed significantly higher arsenic levels. Individuals with febrile seizures experience high oxygen consumption and resulting oxidative stress due to increased metabolic brain activity during the seizure.[7] It has been reported that heavy metals can cause oxidative reactions in biological macromolecules, and metal-related toxicity may lead to oxidative tissue damage.[9,11,12] Redox-active metals such as iron, copper and chromium participate in the redox cycle. In contrast, redox-inactive metals such as arsenic, mercury and cadmium consume antioxidants and enzymes, particularly those containing thiols.[12-14] When arsenic, mercury, and cadmium interact with the carboxyl and sulfhydryl groups of proteins, they increase the production of free radicals, especially ROS. Consequently, it has been reported that metal-induced oxidative stress is a significant factor in the toxic effects of heavy metals.[15-18]

It has been reported that exposure to mercury can occur not only through environmental pollution caused by electronic waste but also through the consumption of fish and ready-made foods containing high fructose corn syrup.[19] Our study did not find any difference in blood mercury levels based on fish

consumption. Mercury not only increases the amount of glutamate and aspartate in the extracellular fluid, thereby sensitizing neurons to excitotoxicity but also causes oxidative cytotoxicity.[20-22] It binds to the carboxyl and sulfhydryl groups of proteins, producing free radicals. Furthermore, it reduces antioxidant levels and disrupts the balance between oxidant and antioxidant capacity.[16,18] In our study, blood mercury levels were found to be expected in both the patient and control groups, and there was no significant difference between them (Table 1). No significant relationship was found between blood mercury levels and seizure duration (Table 2).

Cadmium is a heavy metal that can be harmful to the human body. It is present in cigarette smoke, contaminated food and beverages, and industrial waste produced by batteries or electronic devices.[23,24] Exposure to cadmium can cause the production of free oxygen radicals and inactivate cystine residues containing proteins.[11] Inhaling cigarette smoke is the most significant route of exposure to cadmium. It can damage the vascular endothelium, increase blood-brain barrier permeability, and exacerbate the effects of toxic agents on the brain.[25,26] Cadmium exposure can also lead to the production of various free radicals, such as superoxide, hydroxyl, and nitric oxide.[27] In an animal study, it has been shown to increase lipid peroxidation while decreasing levels of antioxidant enzymes.[18] However, in our study, we found that blood cadmium levels in the patient group were within normal limits and did not differ from the control group. We also found that there was no difference in blood cadmium levels based on exposure to cigarette smoke or stove smoke.

Exposure to arsenic can happen through various sources, such as water, soil, food, and air. It is essential to be cautious and aware of the potential risks associated with exposure to arsenic.[9] In our study, we didn't find any significant difference in the blood arsenic levels of people depending on their drinking water sources (Table 1). Although, the reason behind the high levels of blood arsenic in the patient group is yet to be determined. However, it's worth noting that none of the patients had a blood arsenic level above the normal range (1.17 [0.13-6.55] µg/L [N:0-12µg/L]). Moreover, we found no correlation between blood arsenic levels and seizure duration (Table 2). It's important to note that blood arsenic levels only indicate recent exposure to arsenic and not long-term exposure.

In conclusion, this study significantly found arsenic levels in simple febrile seizures and those without seizures in pediatric patients. However, no difference was found in mercury and cadmium levels. Additionally, there was no correlation between seizure duration and these levels. However, there is a need to do more research to expand upon these findings. The study can serve as a valuable reference point for future investigations.

Ethics Committee Approval: Our study was approved by the Sakarya University Faculty of Medicine Ethics Committee (Date: 29.05.2017, decision no: 16214662/050.01.04/48). The study was carried out following the international declaration, guidelines, etc.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – BE; Supervision BE; Materials – BE; Data Collection and/or Processing BE; Analysis and/or Interpretation – BE; Writing –BE.

Peer-review: Externally peer-reviewed.

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