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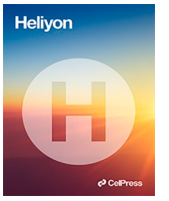

Serum level of vitamin A in febrile children with and without seizure: A comparative study

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ABSTRACT

Objective: The role of vitamins and antioxidants in the febrile seizure (FS) has recently become of interest. The role of Vitamin A in seizure is remained controversial. It may suppress or provoke the seizure. In present study, the serum vitamin A level in febrile patients was compared with febrile seizure children for the first time.

Method: In a cross-sectional study, eighty children aged 6–60 months including 40 febrile children and 40 children with FS were included. Blood samples were obtained, and the serum level of vitamin A and other blood parameters were measured.

Results: Patients were similar in demographic characteristics ($p = 0.06$ for age and $p = 0.41$ for sex). The serum vitamin A level was 0.19 (0.12, 0.25) and 0.22 (0.17, 0.29) milligram per liter (mg/L) in febrile and FS group respectively ($p = 0.33$). In children aged less than 24 months the serum vitamin A level in FS and febrile group was 0.22 ± 0.07 and 0.24 ± 0.12 mg/L respectively ($p = 0.56$). In children aged more than 24 months the serum vitamin A level in FS group was higher significantly in comparison with febrile group (0.25 ± 0.11 and 0.16 ± 0.07 mg/L respectively, $p = 0.01$).

Conclusion: Serum vitamin A level was not different in febrile children with and without seizure. Surprisingly in children aged more than 24 months, the serum level of vitamin A was higher in FS group than in the febrile children. More studies are needed to confirm the present observation.

1. Introduction

Febrile Seizure (FS) is a benign condition that occurs in children aged 6–60 months in association with fever without evidence of intracranial infection, metabolic disorder or any other known cause [1]. FS is the most common type of seizure in children with a prevalence of 2–5% [2]. Although the exact pathogenesis is unknown, but family history, brain disorder and premature birth are known as risk factors [3].

Vitamin A plays different roles in the human body. Vitamin A is involved in vision, reproduction, immunity, cell growth and differentiation [4]. The antioxidant properties of vitamin A have been well documented [5]. One-third of children suffer from vitamin

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A deficiency worldwide [6].

Oxidative stress is involved in the pathogenesis of many disorders including epilepsy, inflammatory diseases and stroke. Children with FS have a higher oxidative stress level than healthy one [7]. Oxidative stress plays a role in the pathogenesis of febrile seizure via mitochondrial damage, cell destruction and damage to the neuronal system [8].

The antioxidant activity of vitamin A, especially in the central nervous system (CNS), can potentially prevent oxidative damage. The association between vitamins and trace elements deficiencies and FS have been investigated previously [9–12]. However, the relationship between serum levels of vitamin A and FS is under studied.

To evaluate the association of serum vitamin A level and febrile seizure in children aged 6–60 months present cross sectional study was carried out for the first time.

2. Patients and method

Present cross-sectional study was carried out in the pediatric clinic of Dr Sheikh Hospital, Mashhad University of Medical Sciences, Mashhad, Iran between March 2021 and March 2022. This study followed the ethical principles of Helsinki. The ethics committee of Mashhad University of Medical Sciences approved the study protocol (code: IR.MUMS.fm.REC.980995). Eighty febrile and FS children aged 6–60 months were selected using non-random sampling. There were 40 febrile children without a history of seizure and 40 febrile children who had experienced their first seizure episode. Following written informed parental consent, 2-mL blood was obtained from the median cubital vein of children. All sampling were done during the first 24 h of hospitalization.

The following data were collected for included patients: Age, gender, height, weight, type of seizure (simple or complex), body temperature, complete blood count test, the serum level of blood sugar, blood urea nitrogen, creatinine, sodium, potassium, calcium, magnesium, vitamin A, history of underlying disease including upper respiratory tract infection, lower respiratory tract infection, gastroenteritis and urinary tract infection. Fever was defined as body temperature 37.5 °C or greater according to axillary measurement. FS was diagnosed according to clinical symptoms and para-clinic data. Simple FS was defined as a generalized, single episode of seizure occurring usually within 24 h of the onset of fever lasting less than 15 min. Complex FS was defined as focal, prolonged (≥15 min), and/or recurrent in the same febrile illness [13]. Patients with a history of seizure, epilepsy, developmental disorders, chronic renal disease and head trauma during the last month were excluded. All blood samples were kept at 18 °C and adequately protected from light until the test was performed. The serum vitamin A level was determined using high performance liquid chromatography (HPLC). A serum vitamin A level below 0.2 mg (mg) per liter (L) was considered as insufficient intake [14].

2.1. Sample size

A sample size of 40 patients in each group and total of 80 patients was considered appropriate to achieve a statistical analysis with adequately power.

Table 1
Demographic and baseline characteristics in 80 febrile children with and without seizure.

Variables	FS group N = 40 (mean ± SD)/Frequency (%)	Febrile group N = 40 (mean ± SD)/Frequency (%)	P value
Age (month)	21.7 ± 14.5	28.5 ± 17.7	0.06*
Height (*Cm*)	86.4 ± 10.5	86.6 ± 12.8	0.94*
Weight (Kg)	12 ± 3.1	13.1 ± 4	0.18*
Sex			0.41#
Male	21 (52.5%)	19 (47.5%)	
female	19 (47.5%)	21 (52.5%)	
Fever Temperature			0.32#
Less than 38 °C	22 (55%)	19 (47.5%)	
Equal or more than 38 °C	18 (45%)	21 (52.5%)	
Hemoglobin			0.51#
Less than 11 g/dl	29 (72.5%)	26 (65%)	
Equal or more than 11 g/dl	11 (27.5%)	13 (32.5%)	
WBC Count			0.31#
Less than 10000 cell/ml	21 (52.5%)	25 (62.5%)	
10000-15000 cell/ml	14 (35%)	8 (20%)	
Equal or more than 15000 cell/ml	5 (12.5%)	7 (17.5%)	
Underlying disease			0.85#
URTI	6 (15%)	6 (15%)	
LRTI	2 (5%)	3 (7.5%)	
GI	15 (37.5%)	16 (40%)	
UTI	3 (7.5%)	5 (12.5%)	
OB	3 (7.5%)	1 (2.5%)	
Others	11 (27.5%)	9 (22.5%)	

FS: febrile seizure, g/dl: gram per deciliter, ml: milliliter, WBC: white blood cell, LRTI: lower respiratory tract infection, URTI: upper respiratory tract infection, GI: gastroenteritis, UTI: urine tract infection, OB: occult bacteremia, SD: standard deviation * independent sample *t*-test, # chi square test.

2.2. Statistical analysis

Data was analyzed using SPSS program version 16 (SPSS Institute, Inc., Chicago, IL, USA). All characteristics of the patients were described as means ± standard deviation (SD), median and interquartile range (IQR) or frequency. Normal distribution was verified using kolmogorov-smirnov test. The relationship between qualitative variables was evaluated using chi-square test. Comparison between two groups was performed using independent sample t testing or its nonparametric equivalent. A p value less than 0.05 were considered significant.

3. Results

3.1. Demographic

There were 40 patients in febrile group and 40 patients in FS group with the mean age of 25.1 ± 16.5 months. There were 40 males and 40 females. Gastroenteritis was the most common underlying disease among patients (n = 31, 38.8%). Fever temperature was more than 38.5 °C in 39 patients (48.75%). The serum level of hemoglobin in 56 patients (70%) was less than 11 g (g) per deciliter (dl). The number of white blood cell (WBC) was less than 10000 cell per microliter (μL) in 46 patients (57.5%). Thirty-one patients (77.5%) were diagnosed with simple seizure. Duration of seizure was more than 15 min in 8 patients (20%). Demographic characteristics are shown in Table 1.

3.1.1. Laboratory data in total population

The serum level of sodium, potassium, urea and creatinine was 135.1 ± 5.3 mEq/L, 4 ± 0.4 mmol/L, 31.4 ± 9.0 mg/dl and 0.45 ± 0.08 mg/dl respectively. The mean of blood sugar and platelet was 94.0 ± 19.1 mg/dl and 291 ± 104 10^9/L respectively. The serum level of vitamin A was 0.22 ± 0.1 mg/L laboratory data in each group were presented in Table 2.

3.1.2. Serum vitamin A level in total population

The serum vitamin A level in the febrile and FS group was 0.19 (0.12, 0.25) mg/L and 0.22 (0.17, 0.29) mg/L respectively (p value = 0.11).

3.2. Comparison between groups according to age

In children older than 24 months, serum vitamin A level significantly was higher in FS group compared to febrile ones (0.25 ± 0.11 mg/L versus 0.16 ± 0.07 mg/L, p value = 0.01). In other age-subgroups, no significant difference was detected between febrile and FS group in serum vitamin A level. The data are presented in Table 3.

The median and IQR of vitamin A in children with simple and complex seizure was 0.22 (0.17, 0.3) mg/L and 0.24 (0.17, 0.28) mg/L respectively (p value = 0.99). Comparison between patients with simple and complex seizure according to age-subgroup (less than 12 months, more than 12 months, less than 24 months, more than 24 months) indicated no difference in serum vitamin A level. Data are presented in Table 4.

4. Discussion

In a cross-sectional study the serum vitamin A level in 80 febrile and FS children were compared. No significant difference was detected in serum vitamin A level in patients with simple and complex seizure. Surprisingly, in children aged 24 months and older, serum vitamin A level was higher in FS patients compared to febrile ones. It may be due to unnecessary use of supplementary vitamins products in many Iranian families in this age group.

FS is a common type of seizure affecting children aged 6–60 months [15]. Antioxidants reduce the incidence of FS and decrease biochemical changes such as oxidative stress markers. Vitamin A, as an antioxidant, play a role in prevention or treatment of several diseases, especially CNS- related diseases [5].

The role of vitamin A in seizure is remained controversial. It has been reported that vitamin A and β-carotene can have some roles in

Table 2
Blood parameters in 80 febrile children with and without seizure.

Variables	FS group N = 40 (mean ± SD)	Febrile group N = 40 (mean ± SD)	P value*
Sodium (mEq/L)	135 ± 5	135 ± 5	0.76
Potassium (mmol/L)	4.0 ± 0.3	4.1 ± 0.4	0.23
BS (mg/dL)	95.1 ± 16.0	92.9 ± 21.3	0.62
Urea (mg/dL)	15.13 ± 3.59	14.25 ± 4.77	0.35
Creatinine (mg/dL)	0.46 ± 0.07	0.44 ± 0.09	0.55
Platelets (/L10^9*)	286 ± 101	296 ± 108	0.67

FS: febrile seizure, mEq: miliequivalent, L: liter, mmol: millimolar, mg: milligram, dl: deciliter, BS: blood sugar, SD: standard deviation * independent sample *t*-test.

Table 3
Serum level of vitamin A in 80 febrile children with and without seizure according to different age subgroups.

Age subgroup		FS group (mean ± SD)	Febrile group (mean ± SD)	P value*
Subgroup 1	less than 12 months	0.23 ± 0.10	0.17 ± 0.07	0.23
	12 months and more	0.23 ± 0.09	0.21 ± 0.11	0.34
Subgroup 2	Less than 24 months	0.22 ± 0.07	0.24 ± 0.12	0.56
	24 months and more	0.25 ± 0.11	0.16 ± 0.07	0.01

FS: febrile seizure, SD: standard deviation * independent sample *t*-test, unit of measurement: milligram/liter.

Table 4
Serum level of vitamin A in 40 children with febrile seizure according to type of seizure and age subgroup.

Age subgroup	Complex seizure (Median (IQR))	Simple seizure (Median (IQR))	P value
less than 12 months	0.15 (0.15–0.15)	0.23 (0.15–0.30)	0.97
12 months and more	0.24 (0.19–0.29)	0.21 (0.17–0.30)	0.99
Less than 24 months	0.22 (0.14–0.26)	0.21 (0.19–0.25)	0.66
24 months and more	0.28 (0.19–0.29)	0.22 (0.12–0.34)	0.61
Total patients	0.24 (0.17–0.28)	0.22 (0.17–0.30)	0.99

Mann-Whitney test, unit of measurement: milligram/liter, IQR: interquartile range.

suppressing some types of seizure including tonic or colonic seizures [16]. On the other hand, vitamin A through retinoid nuclear receptors may have some roles in occurrence and lengthening of seizure attack(s), through gene transcription alteration [17]. Other possible epileptogenic mechanisms of vitamin A can be via alteration of gap junction regulation and opening the neuronal gap junctions. As a result, increasing seizure duration maybe increased [18–20]. According to studies, in Iranian population the mean age of FS is approximately 2 years old [21]. We found in children aged 2 years old serum level of vitamin A is higher in FS group compared to febrile ones.

According to our data in spite of a non-statistically significant difference in serum vitamin A level in febrile and FS children (p value = 0.11), their clinical difference may be important. As we have seen in children aged 2 years and older, the serum vitamin A level statistically significant was higher in FS group. It may support the role of vitamin A in provoking seizure. However, since our study is the first in this topic more researches are needed.

To the best of our knowledge, present study is the first research to evaluate the serum level of vitamin A in febrile and FS children.

The association of vitamins and trace elements deficiency with FS has been noted recently. There are several animal and clinical studies regarding this topic with different results [22–24]. In an animal study it has been reported that vitamin A has an anti-epileptogenic activity in mice and free radical scavenging of vitamin A could be involved in this effect [16]. In a study by Heydarian et al. it has been reported that in spite of normal serum vitamin D level in febrile and FS children, the serum vitamin D level in patients with FS was trending lower [10]. In a review by Ranganathan it has been reported that there was not any evidence to support of routine use of vitamins including folic acid, thiamine, vitamin D or vitamin E in patients with epilepsy [25]. In contrast, in a double blind randomized clinical trial on children aged 6–17 years, it has been reported that use of vitamin E for three months led to more than 60% reduction in seizure frequency in epileptic patients [26]. In a randomized double-blind clinical trial it has been shown that regardless of epilepsy different categories, use of vitamin E had no beneficial effect on seizure even if used for more than three months [27]. A recent randomized clinical trial on patients with epilepsy showed that daily multivitamin therapy (B6, B9, D, E and Q10) for six months led to a significant decrease of seizure frequency [28].

The balance of the oxidant-antioxidant system plays a role in the pathogenesis of many diseases [29]. In a study by Gunes the balance of the oxidant-antioxidant system in febrile seizure was investigated. According to Gunes the level of oxidants in febrile seizure significantly increased and damaged the neuronal system [30].

In a study by Kutluhan, the serum level of antioxidant vitamins (C, E, A) were investigated in pentylenetetrazol-induced epilepsy rats. They reported that the serum vitamin A level in the epilepsy group was not different in comparison with controls. But, the serum vitamin E level was significantly reduced [16]. In present study, there was no significant difference in serum level of vitamin A in febrile children with and without seizure. However, children aged more than 24 months with FS had higher serum level of vitamin A levels than febrile children. Although in recent years, several studies have shown a low level of antioxidants and a high level of oxidants in patients with FS, it should be noted that oxidative stress could be both the cause and effect of a seizure attack [7,31]. This notion can explain why the level of antioxidants is low and the level of oxidants is high in patients with seizure. Therefor the low level of antioxidants should not simply be considered as the cause of seizure.

5. Conclusion

There was not significant difference between febrile and FS children in serum vitamin A level. In children aged more than 24 months, the serum vitamin A level was higher in FS group compared with febrile cases. More studies are needed to establish the role of vitamin A in febrile seizure and confirm our observation.

Ethics statement

The ethics committee of Mashhad University of Medical Sciences approved the study protocol (code: IR.MUMS.fm.REC.980995).

Author contribution statement

Elham Bakhtiari: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Farhad Heydarian: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Fatemeh Azmoudeh: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Maziyar Kaffashbashi, Mohammad Heidarian: Performed the experiments; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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