DOI: 10.37990/medr.1495742 Med Records 2024;6(3):491-5

MEDICAL RECORDS-International Medical Journal

Research Article

Unveiling the Nexus: Is Iron and Sodium Deficiency in Children with Febrile Seizures Risk Factor?

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Abstract

Aim: To examine the connection between the brain and sodium and iron levels in children under age 6.
Material and Method: This retrospective cohort study at Karabuk University Faculty of Medicine included 121 patients divided into three groups: Febril seizure (FS) patients, only fever children without FS, and healthy children. Our study distinguishes itself from other research in this field by its distinctive approach. Various laboratory parameters including sodium, Urea, Creatinine, AST, ALT, RDW, RDW Index, Mentzer Index, Hb, MCV, Ferritin and iron were compared among the groups. Statistical analysis used SPSS software and significance tests.
Results: Significantly lower sodium levels were observed in FS patients and iron levels were notably lower in children with FS. This findings suggest a potential association between lower sodium and iron levels in children with febrile seizures. Thus contributing to unveiling the nexus of brain. Additionaly, elevated AST levels in FS may signify liver function changes. findings suggest a connection between the liver function and brain function. However, urea and creatinine variations were non-significant.
Conclusion: Our findings suggest a potential association between electrolyte levels in children with febrile seizures. Iron plays a crucial role in brain metabolism and is necessary for the activity of certain enzymes involved in neurotransmitter functions. The low levels of sodium and particularly iron in the serum biochemistry of FS patients suggest a connection between these minerals and brain function. Moreover, the observed association between liver function markers and febrile seizures warrants further investigation into the link between liver health and brain function.

Keywords: Febrile seizures, brain connectivity, nexus, iron, sodium

INTRODUCTION

Febrile seizures (FS) are associated with the effect of fever on the brain (1). The increased regional connections are associated with seizures in childhood (2,3). The most prevalent seizure disorder in children is febrile seizures. Predominantly affecting children aged 1 month to 5 years with no prior history of afebrile seizures, arise during febrile illnesses (4). The rise in body temperature can increase electrical activity in the brain, thus accelerating abnormal neuronal responses (5). Understanding the biochemical relationship with the brain may unveil the truth behind these connectivity (6).

The role of iron is essential, especially in facilitating the connectivity of the brain with neurochemical processes. In addition to its role in brain metabolism, iron is also necessary for the activity of certain enzymes involved in neurotransmitter functions (7). Although there have been numerous studies investigating the link between seizures and iron deficiency, the bulk of these researches have been carried out in the Middle East (7). However, this issue continues to be a topic of contention, as conflicting findings persist in the literature. Some studies have suggested a higher prevalence of iron deficiency, in children experiencing febrile seizures (5-7), while others have found no significant association between iron deficiency and febrile seizures (8).

Notably, it is well-established that sodium plays a critical role in regulating nerve transmission and electrical activity in the brain. Research suggests that a decrease in sodium levels may contribute to increased depolarization in nerve cells, potentially leading to seizures (9,10). Therefore, this inference underscores the importance of sodium in neural communication within the brain (11,12). However, there are also studies suggesting contrary findings, which can lead to confusion (13).

CITATION
Deniz Y, Durak U, Dogan E, Ekmen S. Unveiling the Nexus: Is Iron and Sodium Deficiency in Children with Febrile Seizures Risk Factor?. Med Records. 2024;6(3):491-5. DOI:1037990/medr.1495742

Received: 09.06.2024 **Accepted:** 18.08.2024 **Published:** 13.09.2024
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Despite extensive research, the mechanisms underlying febrile seizures remain incompletely understood. Conflicting results and uncertainties have been noted in the literature, contributing to the confusion surrounding this topic. Our study aims to address this gap by investigating the potential relationship between electrolyte imbalances, particularly iron and sodium deficiency, and febrile seizures. Specifically, we aimed to investigate the connection between electrolytes such as sodium and iron with the brain in order to provide further insights into the mechanism of febrile seizures, and to achieve clearer and more reliable results. Additionaly, most studies in the literature have primarily involved comparing two groups, febrile convulsion patients and healthy children (5-8,10). In contrast, our study stands out by comparing three groups (febrile seizure patients, fever-only cases, and healthy children). As far as we know, our study distinguishes itself from other research in this field by its distinctive approach, thereby providing a unique contribution.

MATERIAL AND METHOD

Data Design

The medical records of patients under the age of 6 who presented to the Karabuk University Faculty of Medicine Training and Research Hospital, Department of Pediatric emergency were retrospectively reviewed. We meticulously reviewed medical records, focusing on patients with FS who presented at the pediatric emergency department. The laboratory results and outcomes were systematically detected. Specifically, patients with an R56.0 (Febril seizures) diagnosis code were included in the analysis, encompassing the following International Classification of Diseases (ICD) codes: R56, and R56.9 (Convulsions, other unspecified). Accordingly, initially, 186 patients were identified. However, upon detailed review of the records, patients with afebrile seizures and those aged over 60 months were excluded from the study. Thus, by removing those with incorrect diagnoses, 110 patients with corrected diagnoses were identified. Then, laboratory records of patients with a confirmed diagnosis of FS were examined. We excluded patients with missing laboratory data to ensure data transparency. Subsequently, the e-Nabız patient information system of the Ministry of Health (https://enabiz.gov.tr/) was accessed to identify and exclude patients with chronic illnesses. Thus, an additional 70 patients were excluded from the study. Consequently, a total of 39 patients, confirmed to have febrile seizures without any underlying conditions, were included in the study.

Cohort Classification and Study Groups

The study divided into three groups

Group 1 comprised 42 healthy individuals, Group 2 included 40 patients with fever but no seizures, and Group 3 consisted of 39 patients aged under 60 mounths experienced fever and seizures (total cohort: 121 patients) (female:57; male: 64).

Cohort Classification Strategy

Segmentation for comparative analysis

In a two-group study consisting of patients with fever and seizures (FS) and patients with fever only (Only fever), the variable distinguishing the groups is the presence or absence of seizures, as both groups have fever. Therefore, such a study could investigate how changes in brain electrical activity are affected by iron and sodium levels and explore the relationship between them. However, since it cannot be determined whether changes in iron and sodium levels are due to fever or seizures, the relationship with febrile convulsions may not be conclusively elucidated. This is because the hallmark of febrile convulsion is the occurrence of seizures in conjunction with fever (5). Hence, a third group comprising both febrile and non-seizure patients (healthy children) was added to the study. Patients in this third group were children attending yearly routine health check-ups, diagnosed with Z00.1 (Routine child health examination) according to the ICD coding system, and were matched in age, gender, and number to the FS patient group. This approach allows for a more accurate assessment of the specific effects of FS on various laboratory indicators and outcomes.

Inclusion and Exclusion Criteria

1. **Inclusion criteria of the first group of FS cases:**

- Aged between 6 months and 5 years,
- Experiencing fever and with their first episode of FS,
- Patients who had undergone serum electrolyte and hemogram assessments during febrile seizures, as well as those who had their serum ferritin and iron levels assessed within the last 2 months before and after the onset of seizures.

2. **Exclusion criteria of the first group of FS cases:**

- Recurren FS, the presence of cerebral palsy, electrolyte imbalance caused convulsion, central nervous system infection, chronic and/or genetic disease, metabolic disease, and antibiotic therapy. Patients with seizures lasting >15 minutes were considered to have status epilepticus and were excluded from the study. We initially identified 186 cases of febrile seizures (FS); however, after applying the specified inclusion and exclusion criteria, the number of eligible cases was narrowed down to 39.

3. **Inclusion criteria of the second group of fever without seizures (only fever):**

- The second group was selected from patients diagnosed with R50.9 (Fever, unspecified) and R50.8 (Other specified fever) according to the ICD coding system. They were matched in age, gender, and number to the FS patient group.

4. **Exclusion criteria of the second group of fever without seizures (only fever):**

- FS, Recurren FS, Status epilepticus, the presence of cerebral palsy, Electrolyte imbalance occurred

concomitantly with the disease, the disease triggered the convulsion, central nervous system infection, chronic and/or genetic disease, metabolic disease, and under antibiotic therapy patients.

5. **Inclusion criteria of the third group of healty children:**

- Similar age-gender-number groups admitted to the pediatric outpatient clinics, and had no acute no chronic and no genetic diseases [Diagnosed with Z00.1 (Routine child health examination) according to the ICD coding system].

6. **Exclusion criteria of the third group of healty children:**

- FS, Recurren FS, Status epilepticus, the presence of cerebral palsy, Electrolyte imbalance occurred concomitantly with the disease, the disease triggered the convulsion, central nervous system infection, chronic and/or genetic disease, metabolic disease, and under antibiotic therapy patients.

Statistical Analysis

The data obtained in the study were analyzed using SPSS for Windows (Version 20.0, Statistical Package for Social Sciences) software. Data distribution was assessed based on Skewness and Kurtosis values, confirming a normal distribution. Descriptive statistics for blood parameters in the study included mean and standard deviation values. The relationship between groups and blood parameters was examined using the One-Way ANOVA test with Bonferroni correction, followed by Post Hoc analysis using Tukey and Tamhane tests. Comparisons with p-values less than 0.05 were considered statistically significant.

RESULTS

Changes in sodium, urea, and creatinine values among children in the study, grouped accordingly, are presented in Table 1. Upon analysis, a significant difference was observed only in sodium values among the groups (p=0.00). This significant difference in sodium values was attributed to children with febrile seizures, as their sodium values were found to be lower than both the fever without FS group and the healthy child group. No significant differences were observed in urea and creatinine values (Table 1).

Table 1. Comparison of serum sodium, urea and creatinine values of children

Laboratory parameter	Group-1 (healthy child)	Group-2 (fever-without FS)	Group-3 (febril seizure)	Test* (ANOVA)	p
	mean±SD	mean±SD	mean±SD		
Sodium	138.48± 3.2[a]	138.42± 2.07[a]	136.38±2.07[b]	11.35	0.00
Urea	24.33±8.18	23.55±8.13	25.1±7.38	31.37	0.68
Creatinine	0.33±0.09	0.3±0.1	0.32±0.13	1.14	0.33
ALT	17.57±8.94	16.45±6.13	22.28±23.87	1.69	0.19
AST	36.83±19.44	34.35±9.57	45.03±27.73	3.01	0.05

*One Way ANOVA a-b=there is no difference between values with the same letter; a: results for sodium in group-1 and group 2, b: results for sodium in group-3

The variations in ALT and AST values among the children in the study according to the groups are presented in Table 1. Upon analysis, a borderline significant difference was observed between the groups and ALT and AST values (ANOVA, p: 0.05). It was noted that the group with febrile seizures exhibited higher AST values compared to the other two groups (Table 1).

In Table 2, changes in RDW and MENTZER values of children in the study are presented according to their respective groups. The analysis revealed a significant difference among groups in RDW values (p=0.00). However, this significant difference was attributed to children with only fever group (without febrile seizures), as there was no significant difference in RDW values among children who had experienced febrile seizures. No significant differences were observed in MENTZER and RDW Index values between the groups (with p-values of 0.16 and 0.19, respectively).

Table 2. Comparison of serum RDW, Mentzer and RDW Index values of children

Laboratory parameter	Group-1 (healthy child)	Group-2 (fever-without FS)	Group-3 (febril seizure)	Test* (ANOVA)	p
	mean±SD	mean±SD	mean±SD		
RDW	13.85±0.99[a]	15.49±2.47[b]	14.04±1.4[a]	7.62	0.00
MENTZER	17.13±2.05	16.24±2.46	16.99±2.13	1.87	0.16
RDW INDEX	236.6±27.73	236.2±25.31	211.47±82.1	1.69	0.19
Hb	12.15±1.13	11.85±1.16	12.07±0.9	0.81	0.44
MCV	78.77±4.61	76.4±7.34	78.01±4.62	1.85	0.16
FERRITIN	21.94±12.97	28.01±24.95	19.5±13.9	2.34	0.10
IRON	66.99±34.72[a]	63.23±41.36[a]	51.25±20.75[b]	3.65	0.03

*One Way ANOVA a-b=there is no difference between values with the same letter; a: results for RDW in Group 1 and Group 3; Results for IRON in Group 1 and Group 2, b: results for RDW in Group 2; Results for IRON in Group 3

Changes in iron values among children in the study, categorized by groups, are presented in Table 2. The analysis showed a significant difference among groups in iron values (p=0.03). This significant difference was found to be associated with children who had experienced febrile seizures, as their iron values were lower compared to healthy children. No significant differences were observed between children with fever but without febrile seizures and healthy children (Table 2).

DISCUSSION

The literature on the relationship between low sodium levels and febrile seizures has been characterized by conflicting findings, contributing to ambiguity (11-13). Nevertheless, our study findings, which reveal a significant decrease in sodium levels among children who experienced febrile seizures (FS) compared to both the fever-only (without FS) group and healthy children, are consistent with previous research (6,9,10). This consistency highlights the potential correlation between lower sodium levels and an increased risk of febrile seizures. However, despite these findings, further investigations are warranted to elucidate the precise mechanisms underlying the relationship between sodium levels and seizures, thus contributing to unveiling the nexus of brain.

Our investigation revealed a significant discrepancy among the groups concerning iron values (p=0.03). Specifically, children who experienced febrile seizures exhibited significantly lower iron levels compared to their healthy counterparts. However, no substantial differences were observed between the group of children with only fever (without febrile seizures) and the healthy children group. These findings suggest a potential relationship between iron levels and the occurrence of febrile seizures, consistent with earlier research findings (5,7). Interestingly, upon examining ferritin levels, we found no significant disparities among the groups, aligning with the results of a previous study conducted by Yousefichaijan et al. (8). The observed discrepancy in iron levels between children who experienced febrile seizures and healthy counterparts supports the hypothesis that iron deficiency may contribute to the pathogenesis of febrile seizures. However, the lack of significant differences in ferritin levels suggests that ferritin alone may not be a reliable indicator of iron status in the context of triggering convulsions. Further research is warranted to elucidate the complex relationship between iron metabolism and febrile seizure susceptibility.

Our analysis revealed a significant difference among the groups regarding RDW values (p=0.00). Interestingly, this notable difference was primarily observed in children with only fever (without FS) group. Surprisingly, there was no significant difference in RDW values among children who had experienced febrile seizures. Additionally, no substantial disparities were detected in MENTZER and RDW Index values between the all groups (by the p-values of 0.16 and 0.19, respectively). These research outcomes closely align with the findings reported in a study (7). The significant difference in RDW values in the children-only fever group (without FS) suggests that the elevation in body temperature increases heterogeneity in the size and shape of erythrocytes, to unveiling the nexus of hematologic system. However, the lack of significant difference in RDW values in children who experienced febrile seizures (FS group) suggests that alterations in erythrocyte distribution may not directly influence cerebral electrical activity. Therefore, the original inference drawn is as follows: Fever alters the size and shape of erythrocytes; however, these changes may not directly impact cerebral electrical activity.

Our analysis unveiled a noteworthy trend in AST values among the groups, approaching borderline significance. Significantly, children experiencing febrile seizures displayed elevated AST levels compared to the other two groups. This observation aligns with a similar study where the significance value of AST, which we found to be on the verge of significance, reached statistical significance (10). The elevation in AST levels may potentially signify alterations in liver function associated with febrile seizures. This finding suggests a potential connection between liver function and brain function, indicating the need for further comprehensive investigations to explore this relationship.

In our investigation, variations in urea and creatinine values were observed; however, these differences did not reach statistical significance among the groups (p>0.05). Consistent with our findings, similar studies have also reported no significant differences in these parameters (10,14,15). This implies that urea and creatinine may not play a direct role as contributors to febrile seizures within our study population. Nevertheless, it is imperative to acknowledge the multifaceted nature of febrile seizures and to delve deeper into the exploration of potential contributing factors.

Limitations of the Study

The main limitation of our study is its retrospective nature, which relies on the review of patients' past records. Consequently, imaging techniques that are supported by MRI and enhanced by signal changes could not be utilized.

CONCLUSION

In conclusion, our study sets itself apart by comparing three distinct groups: febrile seizure patients, those with fever alone, and healthy children. Our findings suggest a potential association between lower sodium and iron levels in children with febrile seizures. Thus contributing to unveiling the nexus of brain. Additionaly, our findings suggest a connection between the liver function and brain function, as evidenced by elevated AST levels in FS. Overall, our study enhances our understanding of the complex factors related to febrile seizures.

Financial disclosures: *The authors declared that this study has received no financial support.*

Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *The study strictly adhered to the ethical principles outlined in the Declaration of Helsinki. This study was approved by the Ethics Committee of Karabük University (Ethical Approval Date: 27/02/2023, Ethic Decission No: 2023/1273).*

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