Factors associated with febrile seizures among children

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ABSTRACT

Objective: Febrile seizures are usually benign and are not presented with neurological manifestation. However, complex febrile seizures are presented with recurrence and might require meticulous management. The aim of this study was to evaluate the demographic, clinical, and laboratory parameters of children with febrile seizures and the correlation between these factors.

Methods: In this retrospective study, children presented with febrile seizure in 2019 presented (XXX) were included. Data based on their history, physical examination, and laboratory tests and discharge recommendations were recorded in a checklist. Data were computerized and statistically analyzed using SPSSv25.

Results: Of 77 patients were studied, the mean age of the patients was 29.4 ± 17.6. The mean duration of seizures was 5.09 ± 3.78 min and the mean temperature during seizures was 38.41 ± 0.83 °C. In 44 (57.14%) patients no cause of the fever was recorded. 10 (12.99%) patients had multiple seizures within 24 h 70 (90.91%) seizures presented acutely, without any neurological abnormalities. Routine lab tests include sugar and electrolytes analysis for gastrointestinal infection whereas cerebral spinal fluid analysis can determine the presence of neurological infection. Complex febrile seizures are recurrent in 24 h, with long recovery and longer duration of more than 15 min. Studies have also shown that complex febrile seizures can increase the risk of epilepsy [5, 6].

Pathologically, febrile seizures are characterized as response of an immature brain to fever. Fever is commonly reported as a manifestation of upper respiratory tract or urinary tract infection [4]. These are classified as simple and complex febrile seizures. Simple febrile seizures are presented acutely, without any neurological abnormalities. Routine lab tests include sugar and electrolytes analysis for gastrointestinal infection whereas cerebral spinal fluid analysis can determine the presence of neurological infection. Complex febrile seizures are recurrent in 24 h, with long recovery and longer duration of more than 15 min. Studies have also shown that complex febrile seizures can increase the risk of epilepsy [5, 6].

According to some guidelines, benzodiazepines are used for the treatment of seizures, and prophylactic antiepileptic drugs can prevent recurrent seizures. Diazepam has been recommended by Japanese guidelines for the prevention of recurrent seizures in case of complex febrile seizures [7]. Furthermore, prophylactic treatment after febrile seizures has also been reported to reduce the incidence of epilepsy [8].

In this study we presented the demographic, clinical and laboratory...
data of patients with febrile seizures. Additionally, statistical analysis of the parameters were conducted to determine the correlation with several risk factors, type of seizures, lab findings and recommendation at the time of discharge.

2. Methods

2.1. Patients and study design

In this cross-sectional study, children with seizures and fever referred to (XXX) in 2019 were included. Inclusion criteria for this study was all infants and children aged 6 months to 5 years hospitalized with the diagnosis of seizures based on the doctor’s opinion, lack of known causes of seizures such as meningitis, encephalitis, shigellosis, hypocalcemia, etc. absence of neurological diseases such as epilepsy, cerebral palsy, of seizures such as meningitis, encephalitis, shigellosis, hypocalcemia, etc. absence of neurological diseases such as epilepsy, cerebral palsy, and discharge recommendation.

2.2. Data collection

The data collection questionnaire was carried out by a researcher that included the following information: age, sex, weight, family history of seizures, maternal gestational age, method of delivery, use of powdered milk, use of vitamins and iron, history of seizures, number of seizures, duration of seizures, fever during seizures, type of seizure, drug used in the acute phase of seizures, use of drug in the acute phase, drugs used in the post-seizure stage, treatment for fever reduction, electrolytes, blood sugar, LP (lumbar puncture), white blood cell (WBC) count and discharge recommendation.

Acute seizure was defined as stimulus insensitive rhythmic, uncontrollable and involuntary movement of limbs, face and mouth. WBC count and hemoglobin were obtained from whole blood count data (MDII; Beckman Coulter, Fullerton, CA), blood sugar was analyzed with Analox Instruments, London, UK, erythrocyte sedimentation rate (ESR) was measured with MicroSed system (ELITechGroup, France), C-reactive protein was measured by latex agglutination assay and calcium, sodium and potassium (Ca, Na, and K) were measured using automated instrument Ion Selective Electrode method (Dimension RXL MAX, Siemens/USA).

2.3. Data analysis

The data was computerized and statistically analyzed using SPSSv25. After calculating the proportions and central indices and the appropriate distribution, the results were reported in the form of tables and frequency distribution. P value < 0.05 was considered statistically significant.

This study was approved by the Research Ethics Board of (XXX). Unique identifying number is: researchregistry7291. The methods are stated in accordance with STROCSS 2021 guidelines [9].

3. Results

3.1. Demographic variables and characteristics of the patients

In this study, the 77 patients were studied. The mean age was 29.4 ± 17.6 months (range: 7–75 months) and the mean weight was 13.05 ± 3.73 kg (range: 7 kg–26 kg). The demographic and clinical characteristics of the patients are shown in Table 1.

3.2. Types of seizures

The mean duration of seizures was 5.09 ± 3.78 min and the mean temperature during seizures was 38.41 ± 0.83 °C. Among the causes of fever, in 44 (57.14%) patients, no cause of fever was reported. The frequency distribution of fever-causing disease in children with febrile seizures is shown in Table 2. 49 (63.64%) patients had tonic seizures, 17 (22.08%) patients had tonic-clonic seizures, and 2 (2.6%) patients had loss of consciousness. The frequency distribution of seizures, the medication used in the acute phase and the after the seizure, and treatment of fever is reported in Table 3.

3 (3.9%) patients had higher-than-normal blood sugar and 74 (96.01%) patients had normal blood sugar. 32 (41.56%) patients had leukocytosis and 44 (57.14%) patients had normal white blood cell count and only one patient had leukopenia. 71 (92.21%) patients had normal sodium and 6 (7.79%) patients had less than normal potassium. 39 (50.65%) patients had normal hemoglobin and 38 (49.35%) patients had lower than normal hemoglobin. The frequency distribution of laboratory data of children with seizure fever is given in Table 4.

| Characteristics | Number (%) |
|-----------------|------------|
| Gender          |            |
| Girl            | 37(48.05)  |
| Boy             | 40(51.95)  |
| Nutrition       |            |
| Breast milk     | 37(48.05)  |
| milk powder     | 35(45.36)  |
| Type of delivery|            |
| Natural childbirth| 37(48.05) |
| Cesarean section | 40(51.95) |
| Parent ration    |            |
| Associated      | 23(29.87)  |
| Not associated   | 54(70.13)  |
| Birth status     |            |
| Pre term        | 4(5.19)    |
| Term            | 71(92.21)  |
| Post term       | 2(2.6)     |
| Birthday        |            |
| The first child | 33(42.86)  |
| Second child    | 32(42.56)  |
| Third child     | 9(11.69)   |
| Fourth child    | 3(3.9)     |
| Iron and vitamin supplements | |
| Yes             | 77(100)    |
| No              | 0(0)       |
| History of seizures |        |
| Yes             | 11(14.29)  |
| No              | 66(85.71)  |
| History of convulsive fever |   |
| Yes             | 19(24.68)  |
| No              | 58(75.32)  |
| Family history of seizures |    |
| Yes             | 9(11.69)   |
| No              | 68(88.31)  |

| Characteristics | Number (%) |
|-----------------|------------|
| Blood sugar     |            |
| Normal          | 1(1.3)     |
| Normal>         | 36(46.75)  |
| WBC             |            |
| Normal          | 3(27.27)   |
| Normal>         | 11(14.29)  |
| Ca              |            |
| Normal          | 1(1.3)     |
| Normal>         | 29(38.4)   |
| Mg              |            |
| Normal          | 1(1.3)     |
| Normal>         | 2(2.6)     |
| Na              |            |
| Normal          | 0(0.00)    |
| Normal>         | 0(0.00)    |
| K               |            |
| Normal          | 0(0.00)    |
| Normal>         | 1(1.3)     |
| Hb              |            |
| Normal          | 0(0.00)    |
| Normal>         | 0(0.00)    |
| Hb              |            |
| Normal          | 19(24.68)  |
| Normal>         | 18(23.38)  |
Table 3
Correlation between history of febrile seizure with type of delivery, type of nutrition, recurrence of attacks within 24 h, birth status, developmental status, discharge recommendations, type of seizure, post-seizure drugs and laboratory tests.

|                          | History of convulsive fever | p-value |
|--------------------------|-----------------------------|---------|
|                          | Yes                         | No      |
| **Type of delivery**     |                             |         |
| Natural childbirth       | 10(%)                       | 27(%)   | 0.792  |
| Cesarean section         | 12.99%                      | 35.06%  |         |
| **Type of nutrition**    |                             |         |
| Breast milk              | 13(%)                       | 36(%)   | 0.785  |
| milk powder              | 6(%)                        | 22(%)   |         |
| Evolution status         |                             |         |
| Normal                   | 19(%)                       | 57(%)   | 0.99   |
| Disruptured              | 24(68)                      | 74(03)  |         |
| **Family history of seizures** |                    |         |
| Yes                      | 5(%)                        | 4(%)    | 0.036  |
| No                       | 14(%)                       | 54(%)   |         |
| Birth status             |                             |         |
| Pre term                 | 0(%)                        | 4(%)    | 0.344  |
| Term                     | 19(%)                       | 52(%)   |         |
| Parental ratio           |                             |         |
| Attributed               | 5(%)                        | 18(%)   | 0.780  |
| Not attributed           | 14(%)                       | 40(%)   |         |
| discharge recommendations|                            |         |
| Diazepam during fever    | 8(%)                        | 40(%)   | 0.055  |
| MRI, EEG                 | 11(%)                       | 19(%)   |         |
| Medication used post epilepsy |                        |         |
| Sodium valproate         | 5(%)                        | 4(%)    | 0.005  |
| Phenytoin                | 0(%)                        | 1(%)    |         |
| Medication used post epilepsy |                |         |
| No medicine              | 10(%)                       | 51(%)   |         |
| Type of seizure          |                             |         |
| Simple                   | 12(%)                       | 43(%)   | 0.390  |
| Complex                  | 7(%)                        | 55(%)   |         |
| Occurrence of attacks within 24 h |           |         |
| Yes                      | 3(%)                        | 7(%)    | 0.701  |
| No                       | 16(%)                       | 51(%)   |         |
| Cause of fever           |                             |         |
| No cause                 | 12(%)                       | 32(%)   | 0.882  |
| Gastroenteritis          | 15(%)                       | 41(56)  |         |
| a cold                   | 2(%)                        | 8(%)    |         |
| pneumonia                | 1(%)                        | 3(%)    |         |
| Urinary tract            | 0(%)                        | 1(%)    |         |
| Infection                |                             |         |
| Surgery                  | 0(%)                        | 1(%)    |         |
| WBC                      |                             |         |
| Normal                   | 0(%)                        | 1(%)    | 0.847  |
| Normal                   | 11(%)                       | 33(%)   |         |
| Na                       |                             |         |
| Normal                   | 1(%)                        | 3(%)    | 0.183  |
| Normal                   | 18(%)                       | 57(%)   |         |
| Hb                       |                             |         |
| Normal                   | 0(%)                        | 1(%)    | 0.291  |
| CRP                      |                             |         |
| Normal                   | 12(%)                       | 27(%)   |         |
| Normal                   | 15.58(%)                    | 35.06(%)|         |
| Positive                 | 3(%)                        | 22(%)   | 0.094  |
| Negative                 | 16(%)                       | 36(%)   |         |

3.3. Medications for seizures and gender-based correlation

In 2 (2.6%) girls and 3 (3.9%) boys, diazepam was used in the acute phase to control seizures, in 2 (2.6%) boys phenobarbital and 35 (45.45%) girls and 35 boys (45.45%) were monitored without medication. There was no significant relationship between the drug used in the acute phase and sex, p = 0.367. 5 (6.49%) girls and 4 (5.19%) boys were treated with sodium valproate, 1 (1.3%) boy with phenytoin, and 4 (5.19%) girls and 2 (2.6%) boys with phenobarbital as post-seizure treatment. 28 (36.36%) girls and 33 (43.2%) boys were discharged without long-term drug treatment. There was no significant relationship between the drug used in the post-seizure stage and sex, p = 0.557. In 23 (31.1%) girls and 21 (28.4%) boys, the cause of the fever was not determined. The frequency of patient records by sex of patients is reported in Table 2.

3.4. Correlation between biochemical parameters and gender

21 (27.27%) girls and 11 (14.29%) boys had more white blood cells than normal and 15 (17.8%) girls and 29 (38.4%) boys had normal white blood cells. Sex and WBC count were significantly correlated, P = 0.014. Laboratory data of seizure patients by sex is presented in Table 2.

3.5. Correlation among method of delivery, history of seizure, type of seizure and medication

3 (9.3%) who had recurrent seizures within 24 h had a history of non-febrile seizures. According to p = 0.149, there was no significant relationship between history of seizures and recurrent seizures. 4 (5.19%) patients were discharged with the recommendation of diazepam during fever and 7 (9.09%) patients with the recommendation of MRI and EEG had a history of nonfebrile seizures. According to p = 0.09, there was no significant relationship between discharge recommendations and history of non-febrile seizures. The frequency of a history of nonfebrile seizures by type of delivery, type of feeding, recurrence of attacks within 24 h, birth status, developmental status and discharge recommendations is reported in Tables 3 and 4.
The mean age of children presenting with simple seizures was 28.2 ± 18.18 months and the mean age of children presenting with complex seizures was 16.06 ± 32.4 months. The type of seizure was not significantly associated with age, p = 0.347. The mean age of children who suffered from multiple episodes during a period of illness was 30.7 ± 14.64 months and the mean age of children who did not have multiple episodes was 29.20 ± 18.09 months, which was not significantly different, p = 0.347. The mean age of the CRP positive children was 25.60 ± 17.4 months and 31.53 ± 17.56 months of the CRP negative children, which was not significantly different, p = 0.191. The mean age of the children with ESR positive was 22.56 ± 12.40 months and that of the children with ESR negative was 32.01 ± 18.80 months. The two variables were significantly correlated, p = 0.025. The age of BC positive and negative children was not significantly correlated, p = 0.288. The mean age of the children who underwent LP was 4.3 ± 20.12 months, all negative. The mean body temperature was significantly correlated with the type of seizure, simple or complex, p = 0.139 and the duration and type of seizure was not significantly correlated, p = 0.99.

4. Discussion

Febrile seizures are the most common type of seizure in children. 2.5% Infants and children who are neurologically healthy experience at least one seizure due to a simple fever. Febrile seizures are seizures that occur between the ages of 6 and 60 months with a temperature of 38 °C or greater. Demographic studies have shown that the risk of epilepsy after febrile seizures varies between 2 and 5.2%. There is a brief history of febrile seizures in 10–15% of people with epilepsy.

In our study, 9.51% of children with seizures were boys. In the study by Koppad et al., febrile seizures were more common in boys than in girls [10], however a study by Nezami, Tarhani [11] reported that frequency of female patients was slightly more than males. Our study also showed that family history of seizures was positively related with febrile seizures. Pavlidou and Panteliadis [12] reported that positive family history increases the risk of epilepsy in children by 7.3 times. Sharawat, Singh [4] also found in their studies that children with seizures were more likely to have a recurrence of seizures if there was a positive family history of seizures. In the study by Vitaliti et al., 30% of children with febrile seizures had a positive family history [13]. Also, in the study by Seinfeld et al., the rate of positive family history in children with seizures following fever was 25–40% [14]. In our study, 71% of the children had simple fever and seizures. In the study by Eskandarifar et al., and Hosseini Nasab et al. 81%, and 76% of the patients had simple fever and seizures, respectively [15,16]. In the study by Berg et al., it was reported that 70–80% of the types of fever followed by seizures are

### Table 5

| Age | The drug used post-seizure | p-value |
|-----|---------------------------|---------|
|     | Sodium valproate | Phenytoin | Phenobarbital | No medicine |
| 1yr> | 1                       | 0        | 0            | 6           | 0.853 |
| 1yr< | 8                       | 0        | 1            | 6           | 55    |
| Evolution status | Normal | Disrupted |                |              |
|                  | 9(11.68) | 0(0.0)   | 0(0.0) | 67(97.79) | 60(77.92) | 0.966 |
| discharge recommendations | Diazepam during fever | MRI, EEG |                |              |
|                  | 1(1.3) | 0(0.0)   | 0(0.0) | 67(97.79) | 14(18.18) | 0.116 |
| ESR | Positive | Negative |                |              |
|                  | 1(1.3) | 8(10.39) | 0(0.0) | 4(5.19) | 42(54.55) | 0.268 |
| CRP | Positive | Negative |                |              |
|                  | 1(1.3) | 8(10.39) | 0(0.0) | 5(6.519) | 39(50.65) | 0.116 |
| Type of seizure | Simple | Complex |                |              |
|                  | 5(6.49%) | 4(5.19) | 1(1.3) | 3(3.9) | 46(60.4) | 0.116 |
| Occurrence of attacks within 24 h | Yes | No |                |              |
|                  | 3(3.9) | 6(7.79) | 0(0.0) | 4(5.19) | 57(74.03) | 0.002 |

The mean age of children with recurrent seizures was 38.36 ± 19.85 months and in children without recurrent seizures it was 26.4 ± 15.4 months. There was a significant difference between their mean ages, p = 0.01. The mean age of children with a duration of seizure fever of less than 15 min was 29.71 ± 17.71 months and the mean age of children with a duration of seizures of more than 15 min was 25.33 ± 17.01 months. The two variables were not significantly correlated, p = 0.05 (Table 5).
simple and, in some sources, the range of 60–90% has been reported, which is consistent with the results of our study [17]. Our study reported 38.4 °C. In the study of Mallapa et al., and Miri Aliabad et al. reported the mean rectal temperature was 38.6 and 38.3 °C, respectively [10,18].

In our study, 5.3% of children were preterm. In the study by Koppad et al. and Miri Aliabad et al. 4.5% and 1.3% of preterm children had fever and seizures, respectively [10,18]. In the study by Al-Zwaini et al., the most common cause of fever in children was fever and convulsions, respiratory infection, and in the study by Eskandarifar et al., Khazaiei et al., Respiratory infection and then gastroenteritis were the most common causes of fever in these children [15,19,20]. In the study by Abbasian et al., the most common cause of fever was upper respiratory tract infections (58%) and then gastroenteritis was reported [21]. In our study, the most common cause of fever was unexplained fever (57.14%) followed by gastroenteritis (24.68%) and respiratory tract infection (14.59%). In our study, 3.63% of seizures were tonic and 22% were generalized tonic-clonic. In the study of Inanloo et al., 80% of seizures were generalized [22] on the other hand, in the study of Shinnar et al., only 6% of seizures were generalized [23].

In our study, the number of infants with fever and seizures born by cesarean section was slightly higher than normal delivery (52% vs 48%). In the study by Heydarian et al., children born cesarean had a higher prevalence of seizures with fever [24]. In our study, no significant relationship was found between seizure recurrence in children with fever and seizures and the laboratory factors measured. Therefore, routine laboratory examination is not recommended in all children with fever and seizures to estimate the recurrence of seizures. According to the American Academy of Neurology, routine testing is not recommended in children with simple fever and seizures. In our study, hypokalemia and hypocalcemia were the most common electrolyte disturbances. In the study by Koppad et al., these differences were not statistically significant in both studies [10].

In our study, 3.49% of children with fever and seizures had anemia, which was reported in the study by Bidabadi et al. and Miri Aliabad et al., as 44% and 35%, respectively [18,25]. Despite these differences, some studies have shown that anemia is associated with fever and seizures.

In the Murata et al. study on the effect of acetaminophen on the prevention of seizures during a period of febrile illness, 219 patients were treated with rectal acetaminophen at the onset of seizures and 204 patients did not use any fever medication. Seizures were 9.1% in the group that used acetaminophen and 23.5% in the other group, which was significantly different \( p < 0.01 \) [26]. In contrast to our study, of the 67 patients who did not have recurrences, 49 patients took acetaminophen, but there was no significant relationship between the two. According to the American Academy of Pediatrics (AAP), imaging is not required for all patients with simple acute fever. Evaluation has not been performed on CT scans and IEL, but studies show that radiation exposure on CT scans is associated with the progression of cancer and IEL is associated with risks associated with sedation. CT scans of patients have shown that abnormalities within the cranial structure are rare in neurologically healthy patients presenting generalized thrombosis. There is no evidence that electroencephalography predicts seizure recurrence or non-febrile seizures (epilepsy) in the next two years. According to the American Academy of Pediatrics, cerebrospinal fluid (CSF) analysis is recommended in children under 12 months of age who present with febrile seizures because there are no signs of meningeal stimulation in this age group [27]. Hesdorffer, Chan [28] reported that magnetic resonance imaging of children with febrile seizures without any neurological manifestation is unnecessary.

In our study, 29 (37.7%) patients were advised to undergo EEG or magnetic resonance imaging and 48 (62.3%) patients were advised to take diazepam during fever. Of these 29 patients, 7 (9.09%) had simple seizure and 22 (28.57%) had experienced convulsive seizures, and the other 48 patients who had simple convulsions were recommended to take diazepam during fever. Only one patient was treated with an antiepileptic drug (sodium valproate) and others were discharged without an antiepileptic drug.

Our data is based on a small sample size and discrepancies with the findings of previous studies are due to differences in diagnostic methods and kits used. In order to make study comparable, methods of diagnosis and manufacturer of the kits should be same. This will less effectively predict the sensitivity and specificity of the outcomes.

5. Conclusion

If a history and physical examination suggest a febrile seizure, a blood test is often not needed. The treatment of seizures depends on the recurrence and family history. Further studies, including a larger sample size and genetic analysis, can provide a better conclusion in this regard.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethics approval and consent to participate

This protocol was approved by the Ethics Committee of Lorestan University of Medical Sciences, after obtaining the necessary permission from the University and the Department of Education of Khorraramabad, Lorestan province.

Consent to participate

Under 16 years of age was given by a parent or legal guardian.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Not applicable.

Author contribution

Dr. Alireza Nezami: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Fariba Tarhani: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Gohbad Heidari and Dr. Niloufar Dalvand: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Registration of Research Studies

1. Name of the registry: N/a
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Guarantor

Dr. Fariba Tarhani.

Declaration of competing interest

The authors deny any conflict of interest in any way or by any means during the study. All the fees provided by research center fund and deployed accordingly.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103360.

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