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Original Article

Febrile seizures: is there a significance of chronological ranking of fever and seizure?

Febril nöbetler: Ateş sonrası nöbet zamansal sıralamasının bir önemi var mıdır?

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ABSTRACT

Introduction: Seizures observed in febrile disease periods in healthy children aged from 3 months to 6 years are known as febrile seizures (FS). There is usually a chronological sequence involving seizure following fever in most FS, but some cases may not follow this pattern. This study investigated the chronological relation between fever and convulsion and whether clinical and laboratory findings affect this.

Methods:Patients with FS between 1 December, 2015, and 1 April, 2016, were included in this study. Cases with a regular fever plus seizure chronological sequence were classified as classical FS. Without a regular chronological sequence, fever after seizure, were classified as non-classical FS. The effect on both groups of parameters such as gender, age, height, weight, type of FS (simple or complex), previous history of FS, family history of FS, family history of epilepsy, qualitative c-reactive protein (CRP) and white blood cell (WBC) count were evaluated.

Results:Twenty-seven percent of FS were non-classical and 73% were classical. Negative CRP and low WBC emerged as significant predictors of non-classical FS at binary logistic regression (OR=1.388, 95% CI 1.051-1.834 and OR=9.021, 95% CI 1.298-62.702, respectively). Other factors such as gender, age, height, weight, type of FS, previous history of FS, familyhistory of FS, familyhistory of epilepsyhad no effect in terms of nonclassic FS.

Conclusions:Acute inflammatory response findings such as increased CRP, WBC and fever may not accompany in non-classical FS. Although the diagnosis of FS is correct in such cases, misunderstandings may occur between the physician and parents because of the nomenclature employed.

Keywords: Fever, children, seizure

ÖZ

Giriş: 3 ay-6 yaş arası sağlıklı çocuklarda ateşli hastalık dönemlerinde görülen nöbetlere febril nöbetler (FN)denilmektedir. FN'lerin çoğunda ateş sonrası nöbet zamansal sıralaması görülmekte iken bazı vakalarda bu durum görülmemektedir. Bu çalışmada FN'li hastalarda ateş ve nöbetin zamansal sıralaması ve klinik ve laboratuar bulguların bu zamansal sıralamaya etkilerinin olup olmadığı araştırılmıştır.

Yöntem: 1 Aralık 2015 ve 1 Nisan 2016 tarihleri arasında FN tanısı alan hastalar çalışmaya alındı. Ateş sonrası nöbet zamansal sıralaması gösteren vakalar klasik FN olarak sınıflandırıldı. Ateş sonrası nöbet zamansal sıralaması göstermeyen vakalar ise klasik olmayan FN olarak sınıflandırıldı. Cinsiyet, yaş, boy, vücut ağırlığı, febril nöbet tipi (basit, kompleks), daha önce geçirilmiş FN hikayesi varlığı, ailede FN hikayesi olması, ailede epilepsi varlığı, kalitatif C-reaktif protein (CRP) ve beyaz kan hücre (WBC) sayısından oluşan kategorik ve sayısal değişkenlerinin klasik ve klasik olmayan FN'lere etkisi değerlendirildi.

Bulgular: Hastaların %73'ü klasik, %27'si ise klasik olmayan FN tanısı aldı. Gruplar arası karşılaştırmalarda yalnız WBC sayısı farklı bulundu ve klasik olmayan FN grubunda anlamlı düzeyde düşüktü. İkili lojistik regresyon analizi sonucu negatif kalitatif CRP ve düşük WBC sayısının klasik olmayan FN'ler için anlamlı prediktörler olduğu ortaya çıktı (sırasıyla OR=1,388; 95%CI 1,051-1,834 ve OR=9,021; 95%CI 1,298-62,702).

Sonuç: Klasik olmayan FN'lerde ateş, pozitif CRP yanıtı ve WBC sayısı artışı gibi akut inflamatuar yanıtın göstergeleri görülmeyebilir. Bu tarz vakalarda FN tanısı doğru olsa da tıbbi isimlendirmeden kaynaklanan hekim ve ebeveyn iletişim sorunları doğabilmektedir.

Anahtar kelimeler: Ateş, çocuk, nöbet

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Introduction

Febrile seizure (FS) is defined as generalized tonic clonic seizures in addition to body temperature over 38° C in children between 3 months and 6 years of age. The diagnosis is confirmed by exclusion of central nervous system (CNS) infections and no pre-existing history of epilepsy. The incidence varies depending on the geographical conditions, but is usually between 2% and 4% [1, 2].

Although FS is a benign disease, it causes severe anxiety to parents, who may even fear that their children are dying when they first witness them undergoing seizures [3]. Relieving parental anxiety is therefore as important as the treatment of FS. Although body temperature should be 38° C or over for diagnosis of FS, seizures occur before fever in approximately 1/3 of cases [4]. Since such cases are also referred to as FS (in respect of terminology), this may result in misunderstanding between the parents and physician, with parents insisting that the seizure occurred during the fever free period.

The purpose of this cross-sectional descriptive study was to determine the sequential relation between seizure and fever and whether or not demographic, clinical and laboratory findings affect that relation. We also sought to identify factors in FS cases in which the usual sequence is not observed.

Methods

Patients referred to the pediatric neurology clinic and diagnosed with FS between 1 December, 2015 and 1 April, 2016 were included in the study. Patients referred to the pediatric neurology clinic were examined, and reciprocal interviews were performed with at least one of the parents. Data forms were produced through medical histories obtained from the parents and from patients' medical file records. Seizure and fever history described by parents were confirmed from the patients' medical files. Inclusion criteria were 1) age 3 months to 6 years, 2) diagnosis of simple or complicated febrile seizure within the study period, and 3) normal neurological examination and psychomotor development. Exclusion criteria were 1) psychomotor developmental retardation and/or any neurological disease, 2) birth weight under 2500 g, 3) admission to the neonatal intensive care unit for 3 days or more, 4) previous diagnosis of epilepsy, and 5) FS being comorbid with CNS infection or any other metabolic disorder. Body temperature during seizures was recorded quantitatively and qualitatively by reviewing the medical histories obtained from parents and the hospital medical records. Classification of FS was based upon qualitative body temperature; cases with fever before and during seizure were defined as classical FS, and cases in which body temperature rises after seizure were defined as non-classical FS. Categorical data were defined as gender, seizure type (simple or complex FS), previous history of FS, family history of FS, family history of epilepsy, qualitative C-reactive protein (CRP) and infection focus (acute upper respiratory tract infection, acute gastroenteritis, otitis media and following vaccination). Age (years), body height (cm), body weight (kg) and white blood cell (WBC) count were recorded as numerical data.

Data for sleep and wake electroencephalography (EEG) and computerized tomography (CT) of the brain were recorded if these were performed.

Ethical approval

Ethical approval was taken with date and number respectively 25/07/2018 and 2011-KAEK-27/2018 E.1800090657.

Statistical Analysis

Statistical analyses were performed on SPSS (SPSS Inc. Chicago, IL, USA) version 15 for Windows software. In place of Pearson's chi-square test, independent samples t test and the Mann Whitney U test were used for intergroup comparisons of categorical and numerical data. Independent clinical and laboratory parameters which might affect non-classical FS were evaluated using binary logistic regression analysis. The Hosmer-Lemeshow test was used for goodness of fit of the regression model at $p>0.05$. The risk was expressed as odds ratio (OR) and 95% confidence interval (CI). Statistical significance was set at $p<0.05$ for all calculations.

Results

One hundred five patients diagnosed with FS were enrolled in the study. In contrast to previous studies, FS was classified as non-classical and classical FS in the present research.Twenty-seven percent of FS were non-classical and 73% were classical.

Comparison of categorical data between the two groups revealed a significantly higher incidence of family history of epilepsy in the non-classical FS group (32%) but the relationship was not statistically significant ($p=0.172$). No difference was detected between the two groups in terms of numerical data such as age, body height and weight. However, WBC count was significantly lower in the non-classical FS group compared to classical FS ($p=0.005$), (Table 1).

Seventy-six EEGs (66 during sleep and 10 during wakefulness) were recorded, and no epileptic disorder was detected in any. Irregular posterior background rhythm, considered as a finding for the post-ictal period, was detected in nine patients only. No abnormal finding was detected in 21 brain CTs, except for one case of incidental left frontal encephalomalasia (Table 2).

Binary logistic regression analysis based on the determined risk factors identified negative qualitative CRP and low WBC count as significant predictors for non-classical FS (OR=1.388, 95% CI 1.051-1.834and OR=9.021, 95% CI 1.298-62.702, respectively). Factors including gender, age, body height and weight, type of FS, previous history of FS, family history of FS, family history of epilepsyhad no effect on non-classical FS (Table 3).

Table 1. Descriptive statistics between non-classical and classical FS groups.

	Non-classical FS 27% (n 28)	Classical FS 73% (n 77)	P
Male gender	57%	58%	0.902*
Age (months)	median 24 (range 72.8-6.0)	median 27 (range 72.0-8.0)	0.173**
Height (cm)	mean 86.1 (SD±12.6)	mean 88.7 (SD±10.7)	0.345†
Weight (kg)	median 11.5 (range 30.0-7.6)	13.1 (range 22.4-8.0)	0.077**
Simple FS	68%	80%	0.172*
Positive previoushistory of FS	50%	48%	0.901*
Positive familyhistory of FS	46%	40%	0.571*
Positive familyhistory of epilepsy	32%	19%	0.172*
Focus of infection (count)	URTI 24, AGE 3, postvaccination 1	URTI 63, AGE 13, AOM 1	0.682**
Positive qualitative CRP	29%	39%	0.287*
WBC count	9.05 (SD±3.40)	12.6 (SD±5.93)	**0.005†**

*Pearson chi-square test, **Mann-Whitney U test, †Independent samples t test, AGE; acute gastroenteritis, AOM; acute otitis media, CRP; C-reactive protein, FS; febrile seizure, SD; standard deviation, URTI; upper respiratory tract infection, WBC; white blood cell.

Table 2. EEG and CT data in groupsnonclassic and classic FS.

	Non-classical FS	Classical FS	Total
Sleep EEG	14	52	66
Awake EEG	1	9	10
Brain CT	5	16	21

CT; computerized tomography, EEG; electroencephalography, FS; febrile seizure.

Table 3. Evaluation of the risk levels of the defined factors for non-classical FS by binary logistic regression analysis.

	OR	%95 CI	p
Gender	1.913	0.370-9.885	0.439
Age	1.184	0.969-1.448	0.099
Height	0.819	0.597-1.124	0.216
Weight	1.684	0.859-3.303	0.129
Type of FS	5.056	0.812-31.493	0.082
Previoushistory of FS	0.641	0.891-56.094	0.641
Familyhistory of FS			0.999
Familyhistory of epilepsy			0.999
Qualitative CRP	9.021	1.298-62.702	**0.026**
WBC count	1.388	1.051-1.834	**0.021**

CI; Confidence interval, CRP; C-reactive protein, FS; febrile seizure, OR; odds ratio, WBC; white blood cell.

Discussion

Parents who witness children with no previous health problems undergoing their first seizure often report thinking that their child was dying. Seizures naturally create severe parental anxiety. It has been suggested that this anxiety is associated with a lack of knowledge concerning FS or with a low educational level [5, 6].Even when parents are told that the FS has a good prognosis and that no further tests are required, this still has little effect on their anxiety levels. In most cases, parents insist that the physician request a detailed blood test, EEG and neuro-imaging.

The American National Institute of Health defines FS as seizures with accompanying fever appearing during infancy and childhood with no intracranial infection and identified cause [7]. Due to the problems in identification caused by the requirement for accompanying fever, the International League Against Epilepsy defined FS as seizures associated with a febrile disease, with no reference to the word "fever"[8].

Misunderstandings deriving from the use of the term ‘febrile seizure’ may occur between the physician and parents due to cases in which seizures develop before fever. In this context, the word "febrile" is used to describe an increase in body temperature. Various factors may affect body temperature measurement, including 1- the region of the body (axillary, rectal, oral, tympanic or transcutaneous measurement), 2- tools used for measurement; 3- anti-pyretic drugs and cooler methods used before measurement, 4- the time of measurement (before, during or after seizure), and 5- the age of the child. These factors complicate definite detection, and standard measurement of body temperature in FS becomes problematic [9,10]. Since the majority of incidents of FS occur outside the hospital and body temperature measurement is during the course of seizure is difficult, the data for body temperature in previous studies will not be standard.

Despite detailed investigation of the pathophysiology of FS, no consensus has yet been achieved. Researches have focused on fever, cerebral immaturity, changes in cerebral pH, genetic, environmental and inflammatory mechanisms, and the pathophysiology is now regarded as being multifactorial [11-16]. The generally accepted view is that the proinflammatory cytokines (i.e. IL-1β, IL-6 and TNF-α) which appear as a result of inflammatory response caused by infectious agents are responsible for many clinical and laboratory findings in classical FS [17,18]. Such cytokines are also implicated in various laboratory findings, such as leukocytosis and increased CRP in peripheral blood [19,20]. No increase in blood WBC count and qualitative CRP was detected in the non-classical FS group in this study (Table 3). These findings suggest that a different mechanism may be involved in the pathophysiology of non-classical FS, rather than the cytokine system.

Proinflammatory cytokines are generally produced by mononuclear cells in peripheral blood through stimulation by infectious agents. Cytokines in blood have been shown to increase in the majority of in vivo FS studies [21,22]. In contrast, however, there are also studies reporting no cytokine increase [23]. It has been suggested that, in contrast to common belief, proinflammatory cytokines are produced in various neurons and astrocytes in CNS during febrile disease and even that these give rise to a sudden increase in peripheral cytokines by crossing the blood-brain barrier [12,24-27]. There is still therefore uncertainty concerning the source of proinflammatory cytokines and whether or not these increase in peripheral blood in FS. In the non-classical FS group in the present study, findings of the classic inflammatory response caused by proinflammatory cytokines (fever, and increased CRP and WBC count in blood) were not observed, and seizures were shown to occur in the pre-inflammatory period. This indicates that there may be a local inflammatory response and cytokine production in CNS before the systemic inflammatory response, and that fever and seizures may be triggered through a paracrine effect [28,29].

Limitations

The most important limitation of this study is that blood and CSF cytokine levels were not measured. This represents the most significant problem in terms of corroborating our hypotheses concerning non-classical FS and its pathophysiology.

Conclusion

Increased body temperature or the peak point thereof is usually not specific to the pathogen and does not require any special tests. Quantitative measurement of body temperature is very important in FS, although qualitative evaluation is also of diagnostic assistance in clinical practice. A novel term is therefore needed to replace the term ‘febrile seizure or febrile convulsion’ and to emphasize that such seizures are benign in nature and associated with infection. We believe that a "terminological update" is now required for various medical nomenclatures which may now be regarded as outdated, such as "FS." Further researches are needed to improve communication and confidence between the patients, the patients’ relatives and the physician.

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