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Exploring Inflammatory Status in Febrile Seizures Associated with Urinary Tract Infections: A Two-Step Cluster Approach †

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Abstract: Background: Urinary tract infections (UTIs) are considered common facilitating factors along with other infections in triggering febrile seizures (FS). The main purpose of our study was to identify specific patterns of UTIs, using a combination of inflammatory biomarkers, in order to differentiate UTIs from other bacterial diseases triggering FS. Method: This study included a number of 197 distinct FS events, from patients hospitalized in the Pediatric Clinical Hospital Sibiu, among which 10.2% were diagnosed with UTIs. Results: In one third of the patients with UTI, the symptoms were limited to fever and FS. Using Two-Step cluster analysis, a distinct inflammatory pattern has emerged: higher platelet distribution of the population (PDW), platelet large cell ratio (P-LCR), mean platelet volume (MPV), C-Reactive Protein (CRP) and neutrophil to lymphocyte ratio (NLR). This pattern was associated mainly with bacterial lower respiratory infections. UTIs were highly unlikely in the patients with significantly increased CRP values and normal values of platelet indices. Conclusion. Considering the nonspecific clinical picture of UTIs at an early age, to optimize the management of FS a fast diagnosis of UTI is mandatory. Our study suggests that analyzing the inflammatory biomarkers interlinks (rather than individual parameters) could help identify even oligosymptomatic UTIs patients.

Keywords: febrile seizures; urinary tract infections; inflammatory biomarkers; cluster analysis; laboratory data; C-Reactive Protein; cut-off values

1. Introduction

The International League Against Epilepsy (ILAE) has defined Febrile Seizure (FS) as a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures [1].

Febrile seizure are the most common childhood neurological disorders and an important health problem with potential short and long-term complications [2]. There is a lack of studies regarding the

association between febrile seizures and other bacterial etiologies, such as urinary tract infections. The goal of our study was to identify specific patterns of UTIs, using a combination of inflammatory biomarkers, in order to differentiate UTIs from other bacterial diseases associated with FS.

2. Materials and Methods

This study was conducted at the Sibiu Pediatric Clinical Hospital, as part of a larger project on febrile seizures (see details at [3,4]). The study protocol was approved by the Ethics Committee of the hospital. The study group was represented by a number of 136 patients with 197 distinct febrile seizure events. We used the age criterion according to the revised definition of ILAE, referring to the age range between one month and five years. Simple febrile seizures were defined as generalized seizures lasting less than 15 min and no recurrence within 24 h. Complex febrile seizures were diagnosed based on the presence of at least one criterion from the following: focal appearance, duration over 15 min and multiple seizures within 24 h [1].

Data on patient's general characteristics, seizures' pattern, infectious etiology, biological parameters were analyzed as possible predictors for the UTIs status of febrile seizures children. Analysis was conducted using SPSS v.20 (SPSS Inc., Chicago, IL, USA). Statistical difference was considered for $p < 0.05$.

3. Results

3.1. General Description

We enrolled in the studied group 136 children, with an average age of 23.23 ± 12.43 months and a balanced gender distribution (50.8% boys). There were 197 distinct seizures events, of which 156 (79.2%) with a simple febrile seizures and 41 (20.8%) with a complex pattern. The main seizure duration ranged between 1–5 min and 58.3% from the total febrile seizures events were preceded by temperatures higher than 39 °C. We noticed only in a small number of cases (4.1%) a higher than 72 h time interval from fever occurrence to seizure onset. A more detailed presentation of the results can be seen in Table 1.

Complex febrile seizures were reported in a higher percentage of children from the UTIs group (35%) comparing to the non-UTIs group (gastroenteritis subgroup 25%, acute upper respiratory tract infections (LRTIs) subgroup 21.43%, acute lower respiratory tract infections (URTIs) group 19.01%) (see Figure 1).

3.2. Laboratory Data and Two Step Cluster Analysis Results

When comparing the UTIs group with the non UTI group, individual assessment of values of individual laboratory data parameters did not identify statistically significant differences between groups, except for the C-Reactive Protein (CRP) which had higher values in the UTIs group by comparison to the non UTI group (see more details at [4]).

Further, we performed Two Step Cluster analysis for the whole cohort of patients, using as segmentation variables the inflammatory biomarkers: CRP, neutrophil to lymphocyte ratio (NLR), plachetocrit (PCT), platelet large cell ratio (P-LCR), platelet distribution of the population (PDW), mean platelet volume (MPV), platelet counts (PLT). The clustering method identified four distinct groups of patients. Among resulted clusters a group with distinct inflammatory pattern has emerged: higher PDW, P-LCR, MPV, CRP and NLR. This pattern was associated mainly with bacterial lower respiratory infections-cluster 3. UTIs were highly unlikely in the patients with significantly increased CRP values and normal values of platelet indices. The identified groups profile in terms of demographical and clinical characteristics are presented in Table 2.

Table 1. Description of the demographic and clinical data.

		All 197	**non UTI 177 (89.8%)**	**UTI 20 (10.2%)**	p
Gender	M	100 (50.76)	88 (49.72)	12 (60.00)	0.383
	F	97 (49.24)	89 (50.28)	8 (40.00)	
Age	<6	5 (2.54)	5 (2.82)	0 (0.00)	0.294
	6–12	29 (14.72)	24 (13.56)	5 (25.00)	
	13–24	89 (45.18)	81 (45.76)	8 (40.00)	
	25–36	43 (21.83)	41 (23.16)	2 (10.00)	
	>36	31 (15.74)	26 (14.69)	5 (25.00)	
	M ± SD	23.23 ± 12.43	23.14 ± 12.01	24 ± 16.10	
Temperature	<38	26 (13.20)	20 (11.30)	6 (30.00)	0.106
	38–39	56 (28.43)	49 (27.68)	7 (35.00)	
	39–40	84 (42.64)	78 (44.07)	6 (30.00)	
	40–41	26 (13.20)	25 (14.12)	1 (5.00)	
	>41	5 (2.54)	5 (2.82)	0 (0.00)	
FS episode Type	S	156 (79.19)	143 (80.79)	13 (65.00)	0.099
	C	41 (20.81)	34 (19.21)	7 (35.00)	
Seizure duration	<1	29 (14.72)	25 (14.12)	4 (20.00)	0.843
	1–4.9	93 (47.21)	84 (47.46)	9 (45.00)	
	5–14.9	60 (30.46)	55 (31.07)	5 (25.00)	
	≥15	15 (7.61)	13 (7.34)	2 (10.00)	
Reccurence/24 h	Yes	18 (9.14)	15 (8.47)	3 (15.00)	0.337

Seizure duration was measured in minutes. The p value was computed using Chi-square analysis, Mann-Whitney or Kruskal-Wallis tests (ass appropriate, depending on variables type and distribution).

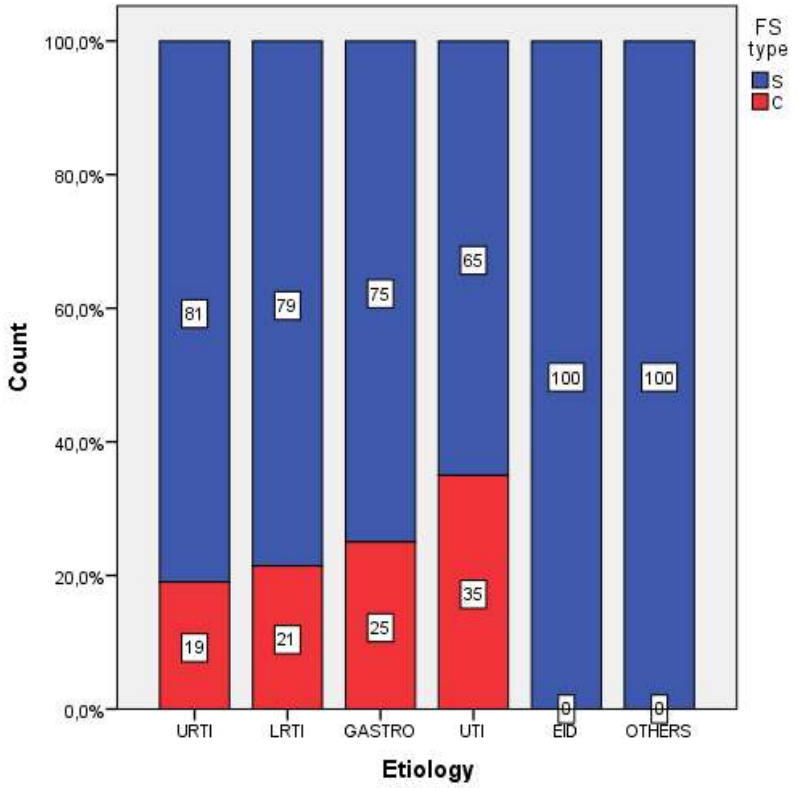

Figure 1. Distribution of simple and complex febrile seizures according to etiology (URTI, LRTI, UTI).

		Cluster 1	Cluster 2	Cluster 3	Cluster 4	*p*
Gender	M	44 (51,16)	26 (47,27)	6 (42,86)	8 (57,14)	0,855
	F	42 (48,84)	29 (52,73)	8 (57,14)	6 (42,86)	
Age	<6	1 (1,16)	3 (5,45)	1 (7,14)	0 (0,00)	0,378
	6–12	11 (12,79)	7 (12,73)	2 (14,29)	4 (28,57)	
	13–24	42 (48,84)	22 (40,00)	4 (28,57)	5 (35,71)	
	25–36	17 (19,77)	16 (29,09)	2 (14,29)	2 (14,29)	
	>36	15 (17,44)	7 (12,73)	5 (35,71)	3 (21,43)	
Temperature	<38	8 (9,30)	8 (14,55)	4 (28,57)	2 (14,29)	0,421
	38–39	28 (32,56)	12 (21,82)	3 (21,43)	6 (42,86)	
	39–40	38 (44,19)	25 (45,45)	4 (28,57)	5 (35,71)	
	40–41	12 (13,95)	8 (14,55)	3 (21,43)	1 (7,14)	
	>41	0 (0,00)	2 (3,64)	0 (0,00)	0 (0,00)	
FS type	S	70 (81,40)	48 (87,27)	9 (64,29)	9 (64,29)	0,096
	C	16 (18,60)	7 (12,73)	5 (35,71)	5 (35,71)	
Seizure duration	<1	10 (11,63)	9 (16,36)	3 (21,43)	3 (21,43)	0,423
	1–4.9	45 (52,33)	22 (40,00)	6 (42,86)	6 (42,86)	
	5–14.9	26 (30,23)	20 (36,36)	2 (14,29)	3 (21,43)	
	≥15	5 (5,81)	4 (7,27)	3 (21,43)	2 (14,29)	
Reccurence/24 h	no	80 (93,02)	50 (90,91)	12 (85,71)	12 (85,71)	0,706
	yes	6 (6,98)	5 (9,09)	2 (14,29)	2 (14,29)	

Seizure duration was measured in minutes. The *p* value was computed using Chi-square analysis, Mann-Whitney or Kruskal-Wallis tests (ass appropriate, depending on variables type and distribution).

The demographic and clinical cluster profile reveals males predominance in cluster 4 (UTI) while females in cluster 3 (respiratory bacterial). The maximum age group incidence is between 13–24 months in patients from both clusters. Most patients in cluster 4 (UTI) have a moderate febrile rise at seizure onset (between 38–39 °C), the percentage being slightly lower in patients with respiratory bacterial infections (cluster 3). In both clusters, most seizures lasted between 1 and 5 min, while 21.43% of patients in cluster 3 and 14.29% of patients in cluster 4 have prolonged seizures (duration > 15 min). Simple febrile seizures predominate in both clusters, representing 64.29% of the cohort. There is a similar percentage of recurrence of seizures in the first 24 h in both clusters.

4. Discussion and Conclusions

We report a UTI prevalence of 10.7%, comparable to that of other studies [6–8]. The results of our study that the most common etiological agents of UTIs are bacteria of enteric origin correlate with the results of other epidemiological studies [9–13]. While analysis of individual inflammatory parameters provided limited knowledge on UTIs in febrile seizures, the cluster analysis identifies four clusters with distinct inflammatory pattern in relation to the etiology of the infectious context profiling a distinctive pattern associated mainly with bacterial lower respiratory infections and a highly unlikely UTIs bacterial etiology based on a higher CRP but with normal platelets indices. Our findings emphasize the practical importance of unsupervised machine learning in hasting the etiology diagnosis for febrile seizures children.

Author Contributions: R.C. conceived, designed, and coordinated the study, performed data acquisition, interpretation of data and drafted the manuscript. I.M. performed data analysis and participated in drafting the manuscript, C.B. provided useful suggestions. B.M.N. participated in analyzing the data, drafting and reviewing the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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