Febrile Seizures

Current Role of the Laboratory Investigation and Source of the Fever in the Diagnostic Approach

Carlos G. Teran, MD,† Marsha Medows, MD,*† Sze H. Wong,† Luis Rodriguez, MD, FAAP,*† and Raymol Varghese, MD*†*

Objectives: The aim of this study was to analyze the value of performing laboratory tests, taking cultures, and imaging, a diagnostic approach for febrile seizures (FSs) still routinely performed despite the American Academy of Pediatrics recommendations not to. Another aim of this study was to identify the most common sources of fever in patients with FSs and to determine whether the occurrence of FSs correlates with the seasons of the year.

Methods: This is a retrospective study that included all patients diagnosed with simple or complex FSs who were seen in the emergency room or inpatient unit from January 2004 to December 2009.

Results: Of the 219 patients included in the study, 135 (61.4%) cases had the etiology of the FS diagnosed. Upper respiratory tract infection, otitis media, urinary infection, and pneumonia were the most common diagnoses attributed to the fever. Leukocytosis was present in 48 (24%) of 219, and neutrophilia in 199 (91%) of 219 cases. Low bicarbonate levels were common among every age group. Only 1 blood culture was positive for *Salmonella*. The incidence of FS was higher during the winter (49.3% of the cases), and it closely paralleled the seasonal variation of viral infections.

Conclusions: Even though laboratory tests, taking cultures, and imaging are performed in daily practice when approaching FSs, the association of FSs with serious infectious disease is rare and usually overestimated. The diagnostic approach should be individualized to each case and correlated with available data like that shown in this study. Parents should be educated with the knowledge that the occurrence of FSs tends to be higher in winter.

Key Words: febrile seizures, laboratory investigation, diagnostic approach

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BACKGROUND

Febrile seizures (FSs) are the most common cause of seizures in the pediatric population, and its prevalence among children in the United States is estimated to be around 3% to 5%.[1] According to the National Institutes of Health, an FS is defined as an event in infancy or childhood, usually occurring between 6 months and 5 years of age, associated with fever but without evidence of intracranial infection or other definable cause.[2]

The presentation of FS has gained importance in the last decades since several studies have demonstrated the association of FS with an increased risk of developing epilepsy.[3–5]

The etiology remains unknown and seems to be complex and multifactorial.[6,7] Infectious agents, genetic factors, vaccines, and even anemia have been proposed as possible causes; however, the exact mechanism of FS remains uncertain.

Respiratory infections, otitis media, and lower respiratory tract infections account for most of the cases per several reports in the literature.[8–10] Even though viral infections are the most common cause of fever associated with FS, the existence of seasonal variation in the incidence of this event was not established in the United States and was assessed in only 2 studies conducted in Japan and the Netherlands, where a predilection for winter was found.[11,12]

The diagnostic approach in the United States is not completely standardized and is usually based on the guidelines and recommendations published by the American Academy of Pediatrics (AAP).[1] The basic laboratory workup and imaging are not recommended in most cases of simple FS, and their use should be individualized for each case.

These recommendations are based on studies demonstrating that the use of hematologic and metabolic profile is of limited value in the initial approach of simple FSs, and the association of abnormalities in electrolytes is very weak.[1,13,14] Similarly, the benefits of performing electroencephalogram, x-rays, computed tomography (CT), or magnetic resonance imaging do not outweigh the disadvantages of radiation, sedation, and additional medical costs.[1,13] Furthermore, a lumbar puncture is indicated only in special situations according to the age and clinical signs of the child.

Despite the recommendations, laboratory workups and imaging are still routinely performed in the emergency room. The possibility of meningitis, invasive bacterial infection, other underlying disorders, and simply the concern for legal issues and pressure from consternated parents are believed to be the most common reasons for the unnecessary tests.

The aim of this study was to demonstrate that laboratory studies are still routinely performed contrary to AAP recommendations and to provide new and detailed laboratory data for the correct interpretation of these tests, which is not previously published. Another aim of the study was to identify the most common sources of fever in patients diagnosed with FS and to determine whether the incidence of FS varies between age groups and seasons of the year.

METHODS

Study Design and Population

This is a retrospective, analytical, and descriptive study consisting of a review of charts from Woodhull Medical and Mental Health Center, a community-based hospital located in Brooklyn, NY, that is affiliated with NYU School of Medicine. We included in the study patients diagnosed with simple or complex FS in the emergency room and/or admitted to the inpatient unit in a period of 6 years, from January 2004 to December 2009.The only exclusion criterion was a change in diagnosis at discharge compared with that of admission.

From the *Department of Pediatrics, Woodhull Medical and Mental Health Center, Brooklyn; and †NYU School of Medicine, New York, NY.
Disclosure: The authors declare no conflict of interest.
Reprints: Carlos G. Teran. MD, 760 Broadway, Brooklyn, NY 11206 (e-mail: carlos.teran@woodhullhc.nychhc.org).
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The protocol was approved by the ethics committee and the institutional review board at NYU Langone Medical Center before reviewing the charts.

Procedures and Statistical Analysis

Chart numbers were obtained from the medical records department at Woodhull Medical and Mental Health Center. All the charts were reviewed through the electronic medical record system QUADRAMED to obtain demographic, clinical, laboratorial, and radiological information from the patients. Statistical analysis was performed using the JMP 6.0 Statistical Discovery Software (SAS Institute Inc, Cary, NC).

Definitions

The diagnosis of anemia was defined as having a hemoglobin level below the 10th percentile for age. The mean corpuscular volume (MCV) was evaluated to determine the type of anemia: an MCV less than the 10th percentile was considered microcytic, an MCV between the 10th and 90th percentile was considered normocytic, and an MCV greater than the 90th percentile was considered macrocytic. The percentile values were based on standardized curves widely used in pediatric practice.[15]

Cell blood count analyses of bicarbonate and calcium levels were based on the reference values from the Johns Hopkins Hospital Department of Laboratory Medicine.[16] Association with vaccination was defined as the occurrence of FS no greater than 7 days after receiving an immunization. According to clinical presentation, complex FSs were defined as having either more than 1 episode within the first 24 hours, an episode duration longer than 15 minutes, or presenting with focalized seizure activity.

As in other northern hemisphere countries, winter was defined as December 21 to March 20, spring from March 21 to June 20, summer from June 21 to September 20, and fall from September 21 to December 20.[17]

RESULTS

A total of 225 patients with the diagnosis of FS were included in the initial review. Six patients were catalogued as having a seizure disorder after neurologic evaluation and were thus excluded from final analysis. Demographic characteristics and classification of the seizures are summarized in Table 1. Complete blood count (CBC) and basic metabolic profile were done in 100% of the cases, and the results are summarized in Table 2. A tendency for low levels of bicarbonate was the most common finding among the children. Blood cultures were obtained from 205 children (93.6%). Of those, only 1 culture (0.4%) was positive for *Salmonella*.

In 206 children (94%), a urine culture was performed. Of those cultures, 15 (6.9%) grew pathogenic organisms, 14 of which were *Escherichia coli* and one of which was *Proteus mirabilis*. Fifty-three children (24.2%) had CSF cultures performed, none of which grew a bacterial pathogen. Lumbar tap was performed in all infants younger than 1 year (39/39) and with complex presentation (18/37). In 1 case, a diagnosis of viral meningitis was done. One hundred eighty-eight (85%) of the patients had a chest x-ray done, 19 (9.5%) of which were reported as abnormal by an experienced radiologist. In order of frequency from the most common, interstitial infiltrates, atelectasis, and lobar consolidation were reported. A head CT scan was performed in 45 patients, including those with complex seizure and 8 patients with simple presentation. No abnormalities on CT were reported in all of them.

In 135 (61.4%) of the cases, the source of fever was diagnosed, and in the remaining 84 (38.6%), source was listed as unknown. In 4 patients, the fever was attributed to a vaccine reaction.

TABLE 1. Demographic, Clinical, and Diagnostic Characteristics of the Population

	Simple (n = 182)	Complex (n = 37)	Total (n = 219)
Age, mean (SD), mo	23 (13.3)	22.3 (12.9)	22.9 (13.2)
Age group, n (%)			
0–11 mo	30 (16)	9 (24)	39 (17.8)
12–23 mo	85 (47)	17 (45)	102 (46.5)
24–60 mo	67 (37)	11 (29)	78 (35.6)
Sex, n (%)			
Male	111 (60)	25 (68)	136 (62.1)
Female	71 (39)	12 (32)	83 (37.9)
Ethnicity, n (%)			
Hispanic	112 (61)	26 (70)	138 (63)
Arabic	3 (2)	2 (5.5)	5 (2.2)
African American	57 (31)	9 (24.5)	66 (30.1)
White	10 (6)	0	10 (4.5)
Season of the year, n (%)			
Winter	86 (47)	22 (60)	108 (49.3)
Spring	40 (22)	6 (16)	46 (21)
Summer	37 (20)	3 (8)	40 (18.2)
Fall	19 (11)	6 (16)	25 (11.4)
Chest x-ray done, n (%)	156 (85)	32 (86)	188 (85.4)
Normal	145 (92)	28 (88)	173 (78.9)
Abnormal	11 (8)	4 (12)	15 (21.1)
CBC, n (%)			
Leukocytosis (septic)	42 (23)	12 (32)	54 (24.6)
Leukopenia	6 (4)	2 (6)	8 (3.6)
Normal	134 (73)	23 (62)	157 (71.6)
Anemia, n (%)			
None	98 (54)	19 (51)	117 (53.4)
Microcytic	41 (22.5)	9 (24.5)	50 (22.8)
Normocytic	43 (23.5)	9 (24.5)	52 (23.7)
Complex seizure, n (%)			
Multiple episodes		34 (91)	
Prolonged duration		3 (8)	

The diagnoses are stratified according to the type of seizure and season of the year and are illustrated in Figures 1 and 2.

The incidence of FS was higher during winter with statistical significance (Fig. 3).

DISCUSSION

The recommendations published and followed by AAP were categorically confirmed in this study. It is clear that the routine performance of basic laboratory and imaging studies is not always necessary in the diagnostic approach of simple FS.

The study of the etiology of FS in the last decades has had a complete turn through the identification of possible predisposing factors and potential infectious agents. Some of these findings were compared and analyzed with the data found in our study.

In terms of laboratory findings, it is interesting to note that 53.4% of our patients had an underlying anemia.

The microcytic type represented 42.7% of anemic patients and 22.8% of all patients. This value is placed between the 6% and 30% found in previous studies conducted in Canada and Italy, respectively.[18,19] This controversial association is still poorly

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TABLE 2. Hematologic and Chemistry Values at Presentation in the ER

	Age Group					
	0–11 mo (n = 39), Mean (SD)		12–23 mo (n = 102), Mean (SD)		24–60 mo (n = 78), Mean (SD)	
	Simple	Complex	Simple	Complex	Simple	Complex
White blood cells, 10^9/L	13.1 (5.8)	15.4 (10)	12.4 (4.9)	15.4 (10)	12.5 (5.8)	14 (5.4)
Neutrophils, %	56 (16)	65 (16)	62.3 (15)	62.2 (12.8)	69.3 (16)	74.1 (11)
Lymphocytes, %	31.8 (17)	20.8 (12.3)	23.2 (13)	24.6 (10.9)	19 (14.1)	16.8 (8.4)
Monocytes, %	10 (4.6)	10.1 (3.6)	12.6 (4.4)	10.6 (4.22)	10.1 (4.5)	7.2 (4.2)
Eosinophils, %	0.5 (0.7)	0.2 (0.4)	0.3 (0.7)	0.2 (0.4)	0.4 (0.8)	0.2 (0.4)
Basophils, %	0.3 (0.7)	0.5 (1)	0.6 (0.9)	0.6 (0.1)	0.1 (0.4)	0.3 (0.5)
Hemoglobin, g/dL	11.7 (0.9)	11.8 (0.7)	11.9 (1.2)	11.6 (0.8)	11.9 (0.8)	11.7 (0.9)
MCV, fL	76.5 (3.5)	77.2 (4.4)	75 (4.5)	74.2 (8.8)	77.2 (4.9)	81.1 (5.8)
Platelets, 10^9/L	346 (127)	425 (86)	326 (103)	360 (129)	308 (106)	400 (136)
Calcium, mg/dL	9.7 (1.0)	9.8 (0.4)	9.8 (0.4	9.6 (0.5)	9.6 (0.5)	9.6 (0.4)
Bicarbonate, mg/dL	17.8 (2.6)	16.5 (1.5)	18.5 (2.2)	17.3 (2.3)	19.4 (2.3)	20.8 (1.8)
Magnesium,* mg/dL	2.4 (0.2)	2.2 (0.07)	2.2 (0.2)	2.4 (0.5)	2.1 (0.2)	2.0 (0.1)
Phosphorus,* mg/dL	5.7 (0.6)	5.8 (0.0)	4.8 (0.5)	4.6 (0.0)	4.8 (0.9)	4 (0.0)

Values are mean (SD).

*Insufficient number of measurements to consider the results reliable.

understood and not applied to the clinical practice.[20,21] Our study lacks a control group and iron studies, making it difficult to interpret the results and give final conclusions.

The role of CBC in the diagnostic approach is not important and can lead to equivocal interpretations and unnecessary further workup in some cases. The presence of leukocytosis in 48 (24%) of 219 cases and especially neutrophilia in 199 (91%) of 219 cases are quite prevalent in CBC and can represent a simple response to the release of steroids and endorphins that are known to occur after an episode of a seizure.[22]

This finding is contradictory because most FSs are associated most of the time with viral infections that cause leukopenia and lymphocytosis.[23] In addition, a normal CBC in children younger than 5 years is predominantly lymphocytic.[16]

A basic metabolic profile was also routinely performed in all our patients but without value in the diagnostic approach. The levels of calcium, sodium, potassium, creatinine, and glucose are not linked with FS. Jaffe et al[14] and Gerber et al[24] and found similar findings in large studies conducted before the AAP recommendations, concluding that the performance of this test is costly and without further benefits in the diagnosis. Nypaver et al[25] found that abnormal serum electrolytes and glucose rarely cause seizure in children, and routine use of these tests in the emergency department is costly and does not contribute to seizure therapy. Other studies had similar conclusions.[26,27]

The presence of a low level of bicarbonate immediately after the occurrence of FS is very common and still not completely understood. The temporal metabolic acidosis state after a seizure can explain this finding, but experimental models in rats on the other hand have demonstrated that the infusion of bicarbonate or the elevation of pH in the brain can stimulate the synapses and trigger a seizure as well.[28,29]

The association between a wide range of infectious agents and the occurrence of FS is well recognized and clearly established in this study; 61.4% of the cases were secondary to an infectious agent, including 4 cases attributed to vaccine reaction (an event involving a reaction to an infectious agent).

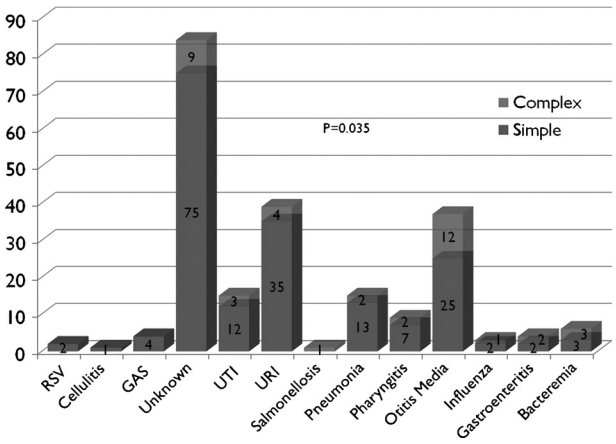

FIGURE 1. Diagnosis of fever according to the type of FS. Contingency table and Pearson test used to calculate statistical significance. Scaled by number of patients.

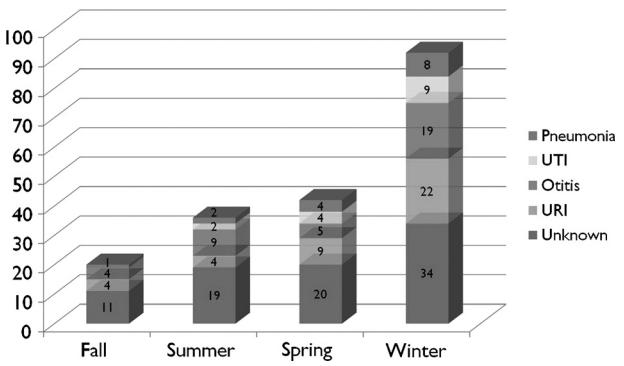

FIGURE 2. Diagnosis involved in the occurrence of FSs according to the season of the year. Contingency table and Pearson test used to calculate statistical significance. Scaled by number of patients.

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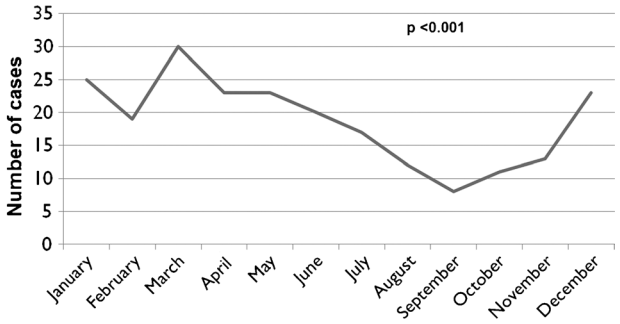

FIGURE 3. Occurrence of FSs during the year.

A broad variety of viral agents is associated with FS.[30–32] This link is variable between studies, and no definite conclusions are available.

One large study conducted in Hong Kong had nasal swab and culture performed on patients with FS. The 5 most common viruses isolated were influenza (17.6%), adenovirus (6.8%), parainfluenza (6%), respiratory syncytial virus (2.7%), and rotavirus (1.3%).[33]

The association between herpesvirus type 6 and FS is the most widely studied, with an incidence varying from 4% to 43% in the literature.[32,34] Contrary to this statement, infantum roseola was not diagnosed in any of our cases.

Infections involving the ears (16.8%), urinary tract (6%), and lungs (6%) accounted for an important proportion of the cases and are comparable with those in the literature.[35,36] Severe bacterial infections such as pneumonia, sepsis, and meningitis were absent in our study, supporting the recommendation to avoid performing laboratory workups for patients with FS. Indeed, because of similar findings in other studies, the AAP recently has published a new recommendation stating that lumbar puncture should not be routinely considered in children from 6 to 12 months of age anymore and is now reserved for those with incomplete immunization status, recent antibiotic use, or presence of suggestive signs of meningitis.[13]

The occurrence of FS does not seem to be associated with a particular virus or bacterium, and we found that its occurrence also follows a seasonal variation closely paralleled to that observed with most common viral infections in childhood. Febrile seizure has a higher incidence during winter (49.3% of the cases) in the United States and similarly in the Netherlands and Japan as reported by 2 studies.[11,12] Therefore, pediatricians are recommended to educate parents that children, especially those with high-risk factors and a history of FS, are more likely to have FS in winter.

CONCLUSIONS

The association of FS with serious infectious disease is rare and usually overestimated. Laboratory investigations are not recommended by the AAP in simple FS but are usually done in daily practice. The diagnostic approach to identify the source of fever should be individualized in each case and correlated with clinical history and physical examination. Interpretation of the laboratory test should be analyzed carefully to avoid unnecessary additional procedures, which can represent a costly permanence in the hospital. Febrile seizures demonstrate a seasonal predilection that should be kept in mind and informed to parents with high-risk children. Finally, we do not intend to generalize the results of this study because clinical practice can vary from hospital to hospital and can be influenced by the institution's guidelines or protocols for the management of FS.

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