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Yield of Lumbar Puncture Among Children Who Present With Their First Complex Febrile Seizure

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WHAT'S KNOWN ON THIS SUBJECT: The association between seizures and ABM is well established. The debate continues regarding how commonly seizures will be the sole manifestation of ABM in a febrile child.

WHAT THIS STUDY ADDS: We have provided an incidence rate of ABM among a large cohort of patients who presented with their first CFS. All of the different seizure features were represented in our cohort.

abstract

OBJECTIVE: To assess the rate of acute bacterial meningitis (ABM) among children who present with their first complex febrile seizure (CFS).

DESIGN AND METHODS: This study was a retrospective, cohort review of patients aged 6 to 60 months who were evaluated in a pediatric emergency department (ED) between 1995 and 2008 for their first CFS. Cases were identified by using a computerized text search followed by a manual chart review. Exclusion criteria included prior history of nonfebrile seizures, an immunocompromised state, an underlying illness associated with seizures or altered mental status, or trauma. Data extracted included age, gender, seizure features, the number of previous simple febrile seizures, temperature, a family history of seizures, findings on physical examination, laboratory and imaging study results, and ED diagnosis and disposition.

RESULTS: We identified 526 patients. The median age was 17 months (interquartile range: 13–24), and 44% were female. Ninety patients (17%) had a previous history of simple febrile seizures. Of the patients, 340 (64%) had a lumbar puncture (LP). The patients' median white blood cell count during a CFS was 1 cell per μL (interquartile range: 1–2), and 14 patients had CSF pleocytosis (2.7% [95% confidence interval [CI]: 1.5–4.5]). Three patients had ABM (0.9% [95% CI: 0.2–2.8]). Two had *Streptococcus pneumoniae* in a culture of their cerebrospinal fluid. Among these 2 patients, 1 was nonresponsive during presentation, and the other had a bulging fontanel and apnea. The third child appeared well; however, her blood culture grew *S pneumoniae* and failed the LP test. None of the patients for whom an LP was not attempted subsequently returned to the hospital with a diagnosis of ABM (0% [95% CI: 0, 0.9]).

CONCLUSION: Few patients who experienced a CFS had ABM in the absence of other signs or symptoms. *Pediatrics* 2010;126:62–69

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KEY WORDS

seizure, complex febrile seizure, meningitis, bacterial meningitis, lumbar puncture, consensus statement, fever evaluation

ABBREVIATIONS

CFS—complex febrile seizure
ABM—acute bacterial meningitis
ED—emergency department
CSF—cerebrospinal fluid
WBC—white blood cell
LP—lumbar puncture
CI—confidence interval

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Febrile seizures are the most common form of childhood seizures, affecting 2% to 5% of all children and usually appearing between 6 months and 5 years of age.[1,2] Febrile seizures are usually categorized as either simple or complex. The features of simple febrile seizures and complex febrile seizures (CFSs) are summarized in Table 1. Approximately 25% to 30% of febrile seizures are classified as complex.[2,3] Complex features (multiple seizures, prolonged duration, or focality) have been associated with an increased risk of recurrent febrile seizures, febrile convulsive status epilepticus, and epilepsy.[4–7]

There is growing evidence that CFSs are associated with multiple factors, which include clinical features,[8] certain viruses,[9,10] genetic[11] and metabolic[12] factors, and possibly structural brain abnormalities.[13] Gurnett et al[11] recently mapped a locus associated with an increased risk for a CFS on chromosome 12. Hesdorffer et al[13] have found minor imaging abnormalities in some patients with a CFS.

Yet, the possibility that a CFS may be the sole presenting sign of acute bacterial meningitis (ABM) remains a major concern.[4,6,14–21]

TABLE 1 Simple Febrile Seizures and CFS

Simple febrile seizures
Self-limiting
Short duration (<15 min)
Tonic-clonic features
No reoccurrence within the next 24 h
No postictal pathology
CFS
Longer duration (>15 min)
May present with series of seizures with limited time interval
New events may reoccur within the next 24 h
Focal seizures, with several possible features
Clonic and/or tonic movements
Loss of muscle tone
Beginning on 1 side of the body, with or without secondary generalization
Head or eye deviation to 1 side
Seizure activity followed by transient unilateral paralysis (lasting minutes to hours, occasionally days)

The association between seizures (of any type, including prolonged, focal, or recurrent) and ABM is well established.[19,22–24] Debate remains regarding how commonly seizures are the sole manifestation of ABM in a febrile child.[15,25]

In 1996, the American Academy of Pediatrics issued a practice guideline regarding the neurodiagnostic evaluation for children who present with their first simple febrile seizure.[26] No such recommendations exist for children with CFSs.

Finally, there are only limited data on the true incidence of ABM among these patients after the introduction of new vaccines against the common causes of ABM (*Haemophilus influenza* type b and *Streptococcus pneumonia*).[25,27–30]

We have provided evidence for the low incidence of ABM in patients who present with simple febrile seizures.[31] The objective of this study was to determine the likelihood of ABM in otherwise healthy children who present to the emergency department (ED) with their first CFS.

METHODS

Study Design

This was a retrospective cohort review of consecutive patients who were admitted to an urban tertiary-care pediatric ED. This ED serves ~50 000 children per year. The study was approved by the Children's Hospital Boston institutional review board.

Study Setting and Population

All patients who presented to the ED between October 1995 and October 2008 and had electronically available physician notes were evaluated for inclusion in this study. During this study period, all physician notes were documented electronically except during 4- to 12-hour system downtimes, which occurred approximately quarterly. Children aged 6 to 60 months who had their first CFS and presented to the ED within 12 hours of their seizure were included. We defined a CFS as described by Waruiru and Appleton,[2] as presented in Table 1. Exclusion criteria included previous nonfebrile seizures or CFSs, a previously diagnosed underlying illness associated with seizures or an immunocompromised state, recent neurosurgical intervention, the presence of a ventriculoperitoneal shunt, or known trauma.

Patients with a generalized seizure that was successfully controlled with anticonvulsant medications given intravenously or rectally before the 15-minute mark were excluded. Although the natural course of some of these seizures would have led to febrile status epilepticus, we had no ability to identify these cases once the seizure was medically controlled.

Study Protocol

Case identification was conducted by using a custom-developed computer-assisted screening tool applied to all eligible physician notes during the study period. The output of the screening tool was reviewed manually by 1 pediatric emergency medicine physician (Dr Kimia).

The Text-Screening Tool

We created a text-screening tool that uses regular expressions for text-matching (ActivePerl 5.8.8.820, Vancouver, British Columbia, Canada). Regular expression-matching provides a more comprehensive search than does a keyword search and is inclusive of various misspelled and mistyped words in the chart (Fig 1).

The module matched a list of expressions in the text. First, a regular expression was applied to every word in every chart, which produced a list of words for the reviewer that included abbreviations, as well as misspelled and mistyped versions of the index

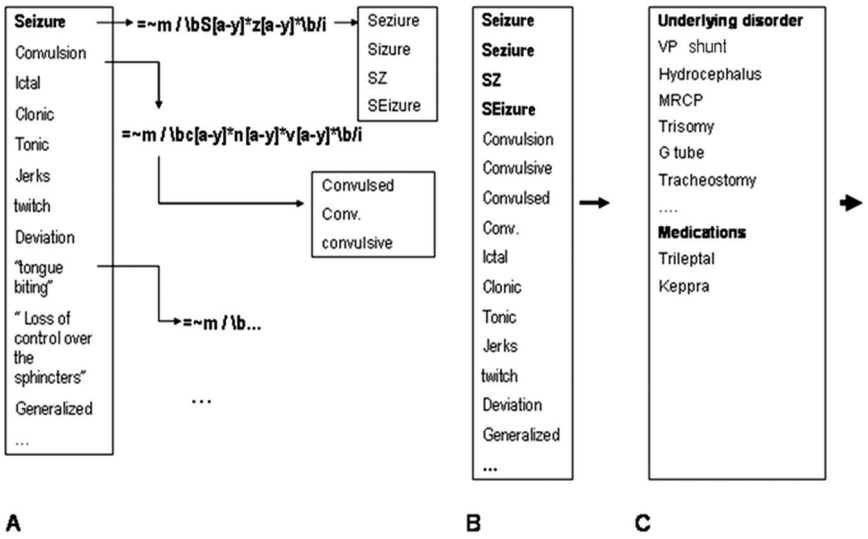

FIGURE 1

Use of a text-search module to detect cases of first CFS. A, The initial word list. B, The use of regular expressions to add misspelled and mistyped words. C, Applying a list of exclusion criteria.

word (Fig 1A). A comprehensive list that included the misspelled, mistyped, and abbreviated words was then applied to the text (Fig 1B). In the next step, a regular expression that addressed negation form was applied to the cases identified, which narrowed the search further. Finally, a previously created list of exclusion criteria was matched against the text, which resulted in a negative score that was applied to the charts. This final step decreased the number of charts that required human auditing (Fig 1C).

Manual Screen of Text-Screening Tool Output

All charts identified by the screening tool were reviewed by 1 of our authors (Dr Kimia).

Data Extraction

Both the trainee and the attending physician notes were reviewed by 3 of the authors (Drs Ben-Joseph, Rudloe, and Kimia). In the case of discrepancies between documentation of a trainee and that of the attending physician, we considered the attending note to be authoritative. For every case that was included in the study, hospital records were reviewed to screen for a second ED visit or hospital admission within 1 week of the index visit.

Each record was screened for features of a CFS. Data that were extracted included age, gender, seizure features, the number of previous simple febrile seizures, temperature, a family history of seizures, vaccination status, current medication (specifically addressing antibiotics), findings on a physical examination, laboratory and imaging study results, and ED diagnosis and disposition. Ten percent of the records were reviewed by a pediatric neurologist from our epilepsy service to assess interrater agreement.

Definitions

Cerebrospinal fluid (CSF) pleocytosis was defined as a CSF white blood cell (WBC) count of $>7/\mu$L. The CSF WBC count for blood-contaminated CSF was determined by using the following correction: corrected CSF WBC count = (CSF WBC count − [CSF red blood cell count/500]).

ABM was defined as (1) growth of a pathogen from any specimen of CSF obtained within 1 week of the visit to the ED for seizure or (2) CSF pleocytosis with growth of a pathogen from any sample of blood obtained within 1 week of the ED visit for seizure. Latex agglutination tests were not routinely used in our facility for the diagnosis of bacterial meningitis.[32]

In cases of a positive blood culture and absence of a CSF cell count (failed lumbar puncture [LP], etc), we defined ABM in accordance with the treating provider. If a diagnosis of ABM was given to err on the side of caution and the patient was treated as having ABM, we identified him or her as having ABM.

Data Analysis

Percentages and confidence intervals (CIs) were calculated for pleocytosis and meningitis rates by using Bayesian credible intervals.

RESULTS

Case Identification

Throughout the study period there were 650 993 ED visits, of which 286 613 were among children aged 6 to 60 months of age. The text-screening tool identified 5744 potentially eligible patients. These charts were then reviewed manually to identify 526 cases of otherwise healthy children who presented with a CFS (Fig 2).

The patients' median age was 17 months (interquartile range: 13–24), and 44% of the patients were female. Vaccination status was available for 429 of 526 patients, of whom 98% reported that their vaccinations were "up-to-date." Of the patients, 156 (29%) were pretreated with antibiotics: 89 patients had received >24 hours of oral antibiotics, and 67 patients were given a dose of parenteral antibiotic before being transferred to our facility for additional evaluation. A sum-

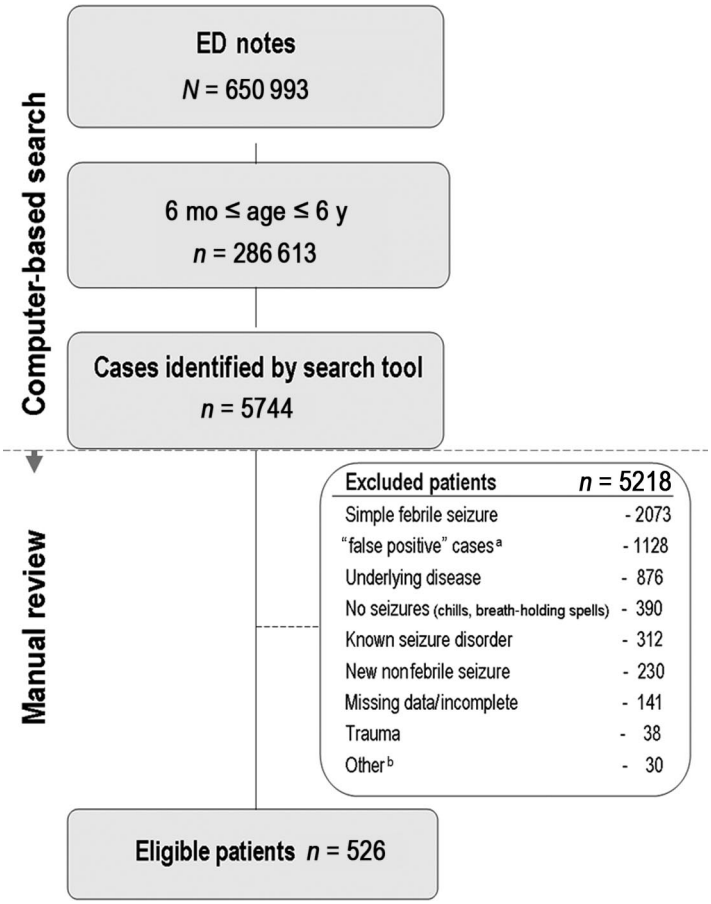

FIGURE 2
Case identification. [a] Cases that were falsely identified by the text-search tool (eg, failure of the tool to identify seizures although they are actually addressed in a negation form ["denies loss of consciousness or seizures," etc]). [b] A variety of individual cases that were excluded for other reasons (such as parents were not sure about time frame, eyes were "deviated" upward rather than lateral, etc).

mary of patient demographics is listed in Table 2.

Among the patients, 384 had 1 feature of a CFS, 122 had 2 features, and 10 had all 3 features (Fig 3). The agreement on classification was $\kappa = 0.88$ for multiple seizures, $\kappa = 0.74$ for laterality, and $\kappa = 0.93$ for duration. The seizure was resolved without intervention in 300 patients (57%). Ninety-nine patients received a benzodiazepine (usually diazepam or lorazepam), 28 patients received phenobarbital, 23 patients received phenytoin/fosphenytoin, and 46 patients were given a combination of anticonvulsant medications to control the seizure. Twenty-eight patients were intubated: 22 of them (78%) because of apnea from anticonvulsant medications and 6 (22%) because of a seizure with poor oxygenation.

Notable physical examination findings were recorded for 65 patients (12%): 5 patients had macrocephaly, 7 patients had petechiae, 14 had a prolonged postictal state, 10 nonsedated nonpostictal patients had an abnormal neurologic assessment, 5 patients had Todd's paresis, and 24 had a combination of the findings listed above. There were 461 patients who had an unremarkable physical examination.

Follow-up clinical information was available (discharge summary, follow-up visits to our facility [in particular, the neurology service], and electroencephalography and imaging studies) for 473 of the 526 patients (90%).

CSF Results

CSF was obtained from 340 patients (64.6%). The median corrected CSF WBC count was 1/μL (interquartile range: 1–2). Fourteen patients had CSF pleocytosis (2.7% [95% CI: 1.5–4.5]) (see Fig 4).

The corrected CSF pleocytosis formula (CSF WBC − [CSF red blood cells/500]) was applied in a total of 9 cases, 2

TABLE 2 Patient Demographics

No. of patients	526
Median age, mo (interquartile range)	17 (13–24)
Female, *n* (%)	44
Recorded previous simple febrile seizures, *n* (%)	
None	436 (83)
A single simple febrile seizure	55 (10)
>1 previous simple febrile seizure	19 (4)
Recorded family history of seizures, *n* (%)	
First-degree relatives	68 (13)
Non–first-degree relatives	61 (12)
Highest recorded temperature, °C (interquartile range)	39.4 (38.6–40.4)
Common infectious diagnosis, *n* (%)	
Fever evaluation	287 (55)
Viral syndrome	89 (17)
Pneumonia	27 (5)
Gastroenteritis	15 (3)
Urinary tract infection	13 (2.5)
Otitis media	71 (13.5)
Admitted patients, *n* (%)	275 (52)

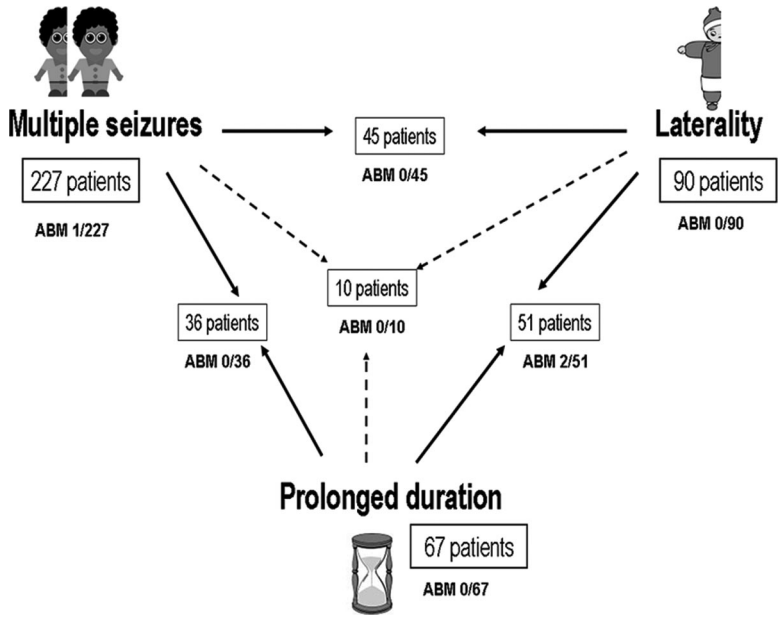

FIGURE 3
CFS by feature.

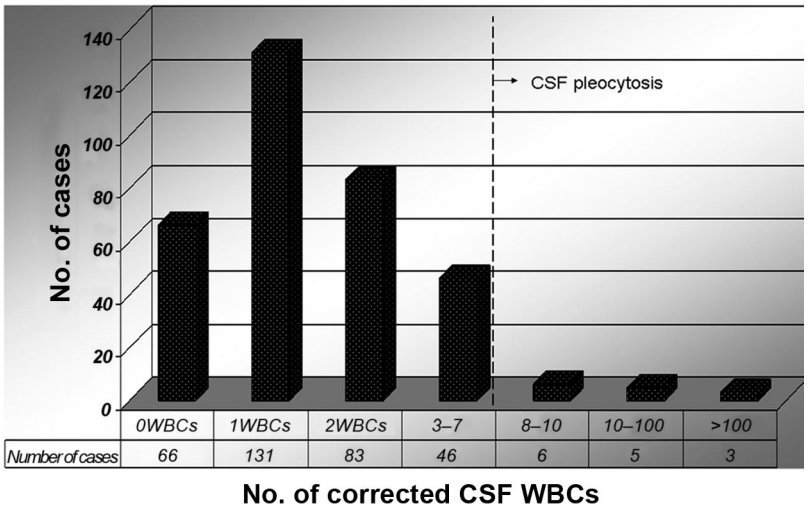

FIGURE 4
Rates of CSF pleocytosis among patients with a CFS.

of which had CSF pleocytosis after correction.

Fourteen patients had CSF pleocytosis; 2 had ABM (see below). Of the remaining 12 patients with CSF pleocytosis, 9 were admitted to the hospital, and 3 were discharged (the CSF WBC count was 8, 10, and 28 cells per μL). All were seen by the neurology service and had no sequelae in follow-up. Of the admitted patients, 4 had presumptive meningoencephalitis on the basis of clinical signs, symptoms, and suggestive findings on EEG. Five had a presumptive diagnosis of viral meningitis.

Bacterial Meningitis

Three patients met study criteria for ABM, all with *S pneumoniae* (0.9%: [95% CI: 0.2–2.7]). Two of the patients presented before the introduction of conjugated pneumococcal vaccines. A contaminant was isolated from 8 specimens (2.4% [95% CI: 1.1–4.7]): 4 nonaureus staphylococci, 3 viridans streptococci, and 1 micrococcus species.

None of the remaining 12 patients with CSF pleocytosis had bacteria recovered from cultured CSF or blood. Three had received previous antibiotic therapy. None of the 186 patients who did not have a LP returned to the hospital with a diagnosis of ABM (0% [95% CI: 0, 0.9]).

Among the 186 patients, 161 (87%) were seen at our facility for follow-up; none had a clinical course of ABM after their initial ED visit.

Description of ABM Cases

Case 1

An 11-month-old male patient was evaluated the previous day for fever and called to return to the ED because of growth from a culture of his blood. After returning, the boy's parents reported that the child was sleepy, and an examination revealed an ill-appearing, toxic, flaccid child with a bulging fontanel and nuchal rigidity. He was responsive to painful stimuli. While he was in the ED, he had an episode of left-leg twitching and right-sided eye deviation. Within a short period he was intubated. His CSF was noted to contain 120 WBCs per μL and Gram-positive diplococci. His course was complicated by a cerebral infarct, and on follow-up he was noted to have mild speech delay.

Case 2

A 4-year-old male patient with a brief history of upper respiratory symptoms was found by his parents to be nonresponsive. Paramedics were called, and the patient was noted to have posturing of the right arm and anisocorea. He was intubated at the scene. His CSF had 866 WBCs per μL, and CSF culture grew *S pneumoniae*. In follow-up, this patient had residual

neurologic deficits, cranial nerve palsy, and a seizure disorder.

Case 3

A 7-month-old female patient presented with 2 short, generalized seizures in a 24-hour period. Her CSF sample was contaminated with blood, and no cell count was ordered. A CSF culture was without growth. She had significant hypocalcemia on arrival, which lead to a diagnosis of rickets. Within 24 hours of admission, her culture of blood grew *S pneumoniae* serotype A19. She was treated for 14 days for a suspected diagnosis of ABM.

DISCUSSION

When a clinician assesses a child with a CFS, he or she reviews the available history, carefully examines the child, and then considers the need for diagnostic testing. Although the introduction of highly effective bacterial conjugate vaccines has significantly reduced the previous probability of bacterial meningitis in a febrile child,[29,30,33] this lower probability does not necessarily correlate with a lower risk in children who experience a CFS. The clinician will wish to understand the rate of ABM that is seen in similar patients when he or she determines whether an LP is likely to be helpful.

The association between seizures (of any type, including prolonged, focal, or recurrent) and meningitis is well established. The rate of seizure among children with ABM has been reported to be from 12% to 27%.[19,22] Recently, Nigrovic et al[23,24] developed and validated a clinical prediction rule for ABM in which the presence of seizure was the only clinical predictor, suggesting its importance.

The question is not whether patients with meningitis may present with seizures but, rather, whether there is a risk of bacterial meningitis among patients who present solely with a CFS. A recent case report in *Pediatrics*[34] described a 12-month-old girl with a simple febrile seizure followed by a CFS. Forty-eight hours after the initial evaluation, she was diagnosed with pneumococcal meningitis, indicating that bacterial meningitis can be present or subsequently develop in a well-appearing patient who presents with simple febrile seizures or CFSs. Teach and Geil[35] reported that none of 243 febrile children aged 3 months to 6 years who had seizures (89% simple febrile seizures; 11% CFSs) had ABM. Other authors have reported an ABM incidence of 2% to 5% overall (simple seizures and CFSs)[36–39] but included patients from before the widespread introduction of conjugated *H influenza* type b or conjugated pneumococcal vaccines. Green et al[15] reported that a seizure did not occur as the only clinical indicator of meningitis in a large series of patients who had bacterial meningitis. Although 23% of their patients had seizures, none lacked other obvious clinical signs of meningitis. Of 115 patients, 105 (91%) were either obtunded or comatose when they were evaluated by a physician for the seizure, and all of the remainder, who had a normal level of consciousness, had focal seizure, recurrent seizures, petechial rash, and/or nuchal rigidity). Because recurrence of seizures is one of the features of a CFS, data regarding rates of ABM in these patients are crucial to clinical decision-making.

In the only previous publication that, to our knowledge, attempted to specifically address a CFS, Seltz et al[25] presented a retrospective case series of 366 patients with a CFS who were identified by *International Classification of Diseases, 10th Revision,* codes searching for "febrile convulsions (R56.0)" and/or different codes that represent a central nervous system infection. LP was performed in 146 (37%) patients. Six patients (5 who received initial care at another hospital and were transferred for additional management) had bacterial meningitis (all *S pneumoniae*), and all were reported to have an abnormal mental status. The total number of patients with a CFS in the referring facilities was unknown, so the authors determined the incidence of ABM with a CFS by reporting an internal rate of 0.3% among patients who presented primarily to their own ED. Their case-identification strategy could have introduced systematic bias that could increase or decrease this estimate. Our study, in which we use a text-search strategy, revealed that 53% (279 of 526) were not given an *International Classification of Diseases* code for febrile seizure.

Patients who present with a CFS are a heterogeneous group of patients. Particular characteristics of a CFS may also be important in determining the risk for ABM. Offringa et al[40] reported an increasing likelihood of bacterial meningitis with longer seizure duration. In a prospective population-based study, Chin et al[4] reported ABM in as many as 17% of children with febrile status epilepticus, defining convulsive status epilepticus as a seizure or series of seizures without recovery of consciousness between seizures and lasting at least 30 minutes (patients with underlying diseases, such as those with ventriculoperitoneal shunts, were included). Joffe et al[37] suggested that patients who had a medical visit within the previous 48 hours, patients who seized on arrival to the ED, or patients with focal seizures are at high risk, in addition to those who have clinically suspicious findings. A much larger study than ours or a case-control study would be required to carefully assess the risk of ABM by each CFS feature. The defining feature of a CFS, with the largest group of children in our study, was more than 1 seizure in 24 hours (227 patients). We had 1 presumed case of ABM in our

cohort of these children with more than 1 seizure in 24 hours as the single CFS feature (0.44% [95% CI: 0.02–2.8]). Because the clinical assessment of these children is rarely complicated by a prolonged postictal state or by sedation from anticonvulsive medication, and the identified risk is low, we concluded that LP should be reserved in this group to patients deemed clinically appropriate.

We acknowledge several limitations to our study. LP was not performed on all patients. Although no patient returned to the hospital with a diagnosis of bacterial meningitis, these patients may have gone to other facilities for their care. For that reason, we presented in our main results an ABM incident based solely on cases in which an LP was performed (3 of 340 patients [0.9% (95% CI: 0.2–2.7)]) as opposed to 3 of 526 for all patients (0.6% [95% CI: 0.15–1.8]).

Our population-reported rate of vaccination was >90%, which is similar to the reported vaccination rates for children in our state (Massachusetts). Providers who practice medicine in countries in which conjugated vaccines for *H influenzae* type b or *S pneumoniae* are not routinely given should be cautious in considering our results in relation to other patient populations.

This high vaccination rate in our study population may limit applicability to patient populations with lower immunization rates. Rates of ABM could be higher when there are differences in causative bacterial strains, patient vaccination status, and differences in the use of resources, as is seen in developing countries.[21,41]

CONCLUSIONS

Few patients with a CFS have ABM in the absence of other signs or symptoms. LP should be performed on the basis of clinical suspicion and additional signs and symptoms that are suggestive of meningitis. Patients whose only feature of a CFS is 2 brief nonfocal seizures in 24 hours seem to be at particularly low risk for ABM.

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College Students Learn About Personalized Medicine in a Unique Manner: *When freshmen enter the class of 2014 at the University of California, Berkeley, they will be offered the opportunity to send in a DNA sample from a cheek swab to inform them about three of their own genetic markers that help regulate their ability to metabolize alcohol, lactose and folates. The testing will be voluntary and confidential with results posted on a Web site using bar code identification. The college plans to then hold lectures on the three genetic markers as well as panels involving philosophers, ethicists, biologists, and statisticians discussing the risks and benefits of personal genomics. According to an article in* The New York Times *(Lewin T, May 19, 2010), not everyone is pleased with the idea of doing genetic testing outside of a medical setting. For example, Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania, comments about the Berkeley program of mass genetic testing and says, "It's a bad precedent to set up mass testing without some sort of counseling support. I'd rather people get their results in a medical setting, where they can ask questions about the error rate or the chances of passing it on to their children, and not just see it posted on some Web site."*

Noted by JFL, MD

Yield of Lumbar Puncture Among Children Who Present With Their First Complex Febrile Seizure

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