ARTICLE:

- **Country:** Canada
- **Funding Sources:** None disclosed.

PURPOSE:

- **Research Question(s):** What is the risk of bacterial meningitis and herpes simplex virus (HSV) encephalitis in children presenting with complex febrile seizures?

DESIGN:

- **Study Design:** Retrospective chart review
- **Dependent / outcome Variable(s):** presence of bacterial meningitis (positive CSF culture, CSF pleocytosis with a positive blood culture, or CSF pleocytosis with a positive CSF latex agglutination test) or herpes simplex virus (HSV) encephalitis (positive CSF HSV PCR)
- **Independent / research Variable:** Complex febrile seizure (fever associated with a seizure that was either prolonged (Q15 minutes), focal, or occurred more than once within 24 hours)

SETTING / SUBJECTS:

- **Research Setting:** Hospital for Sick Children (Toronto, ON, Canada), a large academic tertiary care children’s hospital; emergency and inpatient settings

- **Subjects:**
  - **Study population:** all children 6 months to 6 years; with an ICD-10 discharge diagnosis of febrile convulsion, meningitis, or encephalitis; from January 1, 2002 and December 31, 2006 (i.e. post-Hib/S. pneumo universal vaccincation
  - **Exclusion criteria:** diagnosis of a simple febrile seizure, a history of afebrile seizures, known neurologic disease, immunodeficiency, or trauma
  - **Number (control / intervention groups):** 390 encountering of complex febrile seizures in 366 children; 6 diagnosed with bacterial meningitis;
  - **Demographics:** For all 366 patients: median age 19 months (interquartile range, 14-28 months); 48% under 18 months old; 185 hospitalized; 75 referred; 57% were males; 36% with history of febrile seizure.
Attrition: There was no attrition as this was a retrospective chart review; however, some patients were excluded due to duplicate records or incomplete data, in addition to the aforementioned exclusion criteria.

METHODS:
- Interventions: No interventions performed.
- Study Groups: Rates of CNS infection were compared within each of the following 4 groups:
  - (1) patients transferred from a community hospital (referred group) versus those whose initial presentation was to their own hospital’s emergency department (non-referred group);
  - (2) patients with an abnormal mental status examination versus those with a normal mental status;
  - (3) children 18 months or younger versus children older than 18 months of age; and
  - (4) children presenting with a first febrile seizure versus those with a history of febrile seizures
- Instruments: None
- Data Collection: Does not indicate who specifically performed the chart review.

DATA ANALYSIS:
- Level of Data: Categorical
- Statistics Used: Rates of bacterial meningitis and HSV encephalitis were calculated, and Fisher exact test was used to calculate 95% confidence intervals (CIs). All comparisons were analyzed using either the chi^2 test or Fisher exact test for comparison of proportions.
- What, if any, variables were controlled for? None.

RESULTS:
- Brief answers to research questions: The overall rates of bacterial meningitis and HSV encephalitis in children presenting with complex febrile seizures were low (1.5% and 0.3%, respectively); this answers the original question.
  - NB, that only 37% (146) of the 366 patients had an LP performed; the diagnosis of meningitis or encephalitis was based on CSF findings; the rates based on patients who had LPs performed are closer to 4% and 0.7%, respectively.
- Additional findings:
  - Rate of CNS infection was significantly LOWER in non-referred patient encounters (0.3%; 95% CI, 0.0-2.0) than in referred patient encounters (8.0%; 95% CI, 3.4-16.7) (P < 0.001).
    - NB: selection bias
  - Rates of CNS infection were HIGHER in children with an abnormal mental status examination (n=119). Seven (6%) of the 119 patient
encounters with a decreased mental status had CNS infection as compared with none in those with a normal mental status examination (P < 0.001).

- Rate of CNS infection in encounters in infants <= 18 months was the SAME as the rate in infants older than 18 months (P = 0.40).
  - i.e. NOT statistically different
- In patients with a history of previous febrile convulsions, no patient (0/140; 0.0%; 95% CI, 0.0-3.2) was diagnosed with a CNS infection compared with 7 out of 250 (2.8%; 95% CI, 1.2-5.8) patients presenting with a first febrile seizure (P = 0.09)
  - i.e. NOT statistically significant.

**Other possible explanation for findings:** Referred patients had a higher rate of infection; selection bias? Epidemiology may have changed rates of meningitis due to immunization (however, this shouldn’t alter HSV encephalitis rates if the immunizations are for Hib and S. pneumo). They agree that patients with meningitis are more likely to have seizures that are complex; the question is whether with the changed epidemiology of meningitis (decreased incidence) whether a complex seizure should be considered a strong marker or risk factor of CNS infection. They illogically state that:

- Although previous data have shown that seizures due to meningitis usually have complex features, these findings may no longer be applicable as the epidemiology of bacterial meningitis has changed.
  - It isn’t clear how a decreased incidence of bacterial meningitis invalidates the fact that seizures due to meningitis usually have complex features (although it might decrease the likelihood that of all comers with complex seizures, one is less likely to have meningitis).

**Limitations:** Retrospective review; small sample size. Low (37% total) LP rate. Statistics on rates of meningitis calculated from total identified cases of complex febrile seizures, most of whom did not receive an LP, and a CSF-based definition of bacterial meningitis or HSV encephalitis (which underestimates the rates). They then start talking about meningoencephalitis on page 496 (presumably meaning meningitis and encephalitis). No follow-up (they presumed that patients with CNS infections would return to that hospital). Large proportion (34%) with a prior history of febrile convulsions. Usage of ICD codes as opposed to manually reading through charts (Kimia 2010 found that approximately 50% of patients with febrile seizures were not given an ICD code for febrile seizure).

**IMPLICATIONS FOR PRACTICE:**

- **Applicable to this clinical practice:** Maine Medical Center is a relatively large tertiary academic hospital for the region, but is not a children’s hospital, which is where the study was performed. They see more children, have higher referral rates and likely have a higher incidence of febrile seizures. Do we have the same vaccination rates as does Canada? Depends on funding for universal vaccinations (vaccination rates have been falling off in Maine since approximately 2009).
• Feasible (cost, resources, etc): The intervention would be doing less lumbar punctures in patients with complex febrile seizures and this probably warrants further study.

• Clinically Relevant: It is clinically relevant to change the thresholds for performing lumbar punctures in pediatric complex febrile seizures and needs further study.

LEVEL OF EVIDENCE / DECISION FOR USE:
• _X_ Background     Consider Replication     Ready for use

• Level of Evidence:
  Ia  Evidence obtained from meta-analysis of randomized controlled trials
  Ib  Evidence obtained from at least one RCT
  IIa Evidence obtained from at least one well-designed controlled study without randomization
  IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
  X  III Well-designed non-experimental studies
  IV  Expert committee reports, opinions of experts