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Inpatient admission for febrile seizure and subsequent outcomes do not differ in children with vaccine-associated versus non-vaccine associated febrile seizures

Sara Y. Tartof*, Hung Fu Tseng, In-Lu Amy Liu, Lei Qian, Lina S. Sy, Rulin C. Hechter, S. Michael Marcy, Steven J. Jacobsen

Department of Research & Evaluation, Kaiser Permanente Southern California, USA

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ABSTRACT

Introduction: Recent data suggest that the risk factors for febrile seizure (FS) can differ depending on whether the FS was vaccine-associated (VA) or not. As such, there also may be differences in the risk of inpatient admission and/or the incidence of FS-related subsequent outcomes following the index FS depending on whether it was VA or non-vaccine associated (NVA). This could have useful clinical implications including caregiver education and planning for follow-up care.
Methods: This cohort study consisted of 3348 children who experienced an index FS between 6 months up to 3 years of age from July 1, 2003 through December 31, 2011. The index FS was determined to be VA-FS or NVA-FS; inpatient admission for FS, recurrent FS, and diagnosis of epilepsy were compared between exposure groups. Hazard ratios and relative risk estimates comparing between VA-FS and NVA-FS were estimated by Cox proportional models and Robust Poisson regression models, adjusted for race, sex, age at first FS, birth weight, gestational age, maternal age, and 1- and 5-min Apgar scores.
Results: The mean age at index FS was 1.5 years; the mean length of follow-up was 2.3 years. Of all index FS, 383 (11.4%) were VA and 2965 were NVA. Among index FS, 264 (7.9%) were admitted as inpatients. Subsequently, 703 (21.0%) children developed at least one recurrent FS, where the number of recurrences ranged from 0 to 9 events. Overall, 144 (4.3%) children were diagnosed with epilepsy during the follow-up period. In adjusted analyses, VA-FS did not differ in the risk for any of the outcomes of interest compared with NVA-FS.
Discussion: The risk of hospitalization for index FS or select subsequent FS outcomes did not differ between VA or NVA-FS. This suggests that the follow-up care of children with VA-FS does not warrant attention beyond that for NVA-FS.

1. Introduction

Febrile seizures (FS) are the most common seizures in childhood and typically occur with a peak incidence in the second year of life. FS are defined as seizures that occur in febrile children from 6 months to 5 years who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures [1]. Febrile seizures are classified as simple or complex. Simple febrile seizures are generalized, last less than 15 min, and occur once in a 24-h period. Complex febrile seizures may have focal features, last longer than 15 min, and recur within a 24-h period. FS affect 2–5% of the pediatric population [1]. Risk factors include febrile infections and some vaccinations [2–10], genetic factors, lower gestational age and low birth weight [1,11,12].

The long-term morbidity and mortality associated with FS is extremely low. However, children who have one FS can have recurrences. Approximately 30% of children with first FS will have a second episode, often occurring within 2 years of the index event [13]. Known risk factors for recurrence include younger age at first FS, family history of FS, and low temperature of fever at first FS [14]. Subsequent diagnosis of epilepsy has also been investigated. The risk of epilepsy after simple FS is estimated to be only slightly higher than the risk in the general population [15]. Those with

* Corresponding author at: Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles, 2nd Floor, Pasadena, CA 91101, USA. Tel.: +1 626 564 3001; fax: +1 626 564 3409.
E-mail addresses: sara.y.tartof@kp.org, startof@gmail.com (S.Y. Tartof), Hung-fu.X.Tseng@kp.org (H.F. Tseng), Amy.L.Liu@kp.org (I.-L.A. Liu), Lei.X.Qian@kp.org (L. Qian), lina.s.sy@kp.org (L.S. Sy), Rulin.C.Hechter@kp.org (R.C. Hechter), smmarcy@labiomed.org (S.M. Marcy), steven.j.jacobsen@kp.org (S.J. Jacobsen).

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multiple simple FS, family history of epilepsy, or age <1 year at first FS have higher rates of epilepsy diagnosis [15–18].

Recent data demonstrate that the risk factors for FS can differ depending on whether the FS was vaccine-associated (VA) or not, suggesting that there may be immunogenetic differences between FS triggered by vaccines versus other causes [19]. As such, there also may be differences in the risk of inpatient admission for the initial FS or in subsequent outcomes of the FS depending on whether the FS was VA or non-vaccine associated (NVA). This could have useful clinical implications including caregiver education and planning for follow-up care. Therefore, we conducted a cohort study among children with a first FS between 6 months and 3 years of age to determine if the rates of inpatient admission, FS recurrence, or subsequent diagnosis of epilepsy differ between children with first FS that is VA versus NVA.

2. Methods

2.1. Source population

The study included members of Kaiser Permanente Southern California (KPSC) health care system. KPSC is a pre-paid, integrated health care organization with 3.6 million members who are representative of the socioeconomic and racial diversity of the area population [20]. KPSC uses electronic medical records (EMR) to integrate medical information including diagnostic and procedure codes, vaccinations, and medications and laboratory results from all outpatient, emergency department (ED), and inpatient settings. When care is received from non-KPSC providers, visit details are captured through claims data which are required for reimbursement. Childhood vaccinations are offered at no charge for KPSC members and outside administration of vaccines is not common.

2.2. Study population

Many of the details of the study cohort have been described previously [19]. Briefly, the study cohort consisted of 3348 children who experienced a first (index) FS between 6 months and 3 years of age from July 1, 2003 through December 31, 2011, as this age range represents the period during which the majority of FS and vaccinations occur. Determination of FS was by International Classification of Diseases-Ninth Revision (ICD-9) codes (ICD-9 780.31, 780.32) identified in inpatient and ED settings [2,21]. Exclusion criteria were applied from birth and included seizures with fever in children who had previous evidence of intracranial infection, history of afebrile seizures, metabolic disturbances, previous neurologic insults, or known central nervous system abnormalities. Determination of exclusion criteria was based on ICD-9 codes identified in inpatient, ED, and outpatient files (codes, Appendix A).

Continuous membership was required from birth to censorship (termination of membership, 5 years age, death, or end of study [December 31, 2012]). A 31-day gap in membership was permitted from ages 6 months to 5 years; a 61-day gap in membership was permitted for ages 0–6 months.

2.3. Exposures of interest

The main exposure of interest was whether the index FS was a vaccine-associated febrile seizure (VA-FS), or a non-vaccine associated FS (NVA-FS). VA-FS were defined as those that occurred from day 0 (day of vaccine administration) to day 15 following receipt of vaccines recommended for children 6 months through 3 years of age by the Advisory Committee on Immunization Practices. NVA-FS were defined as all other FS occurring outside the 0–15 day follow-up period post-vaccination. For vaccines administered during overlapping periods (i.e. more than one vaccine in the 0–15 day risk period), the follow-up period began at the time that the first vaccine is administered and ended 15 days following receipt of the last vaccine in the overlapping period.

To evaluate the effect of other factors that may be associated with the study outcomes and which have been associated with VA-FS [19], individual-level risk factors of race, sex, age at first FS, birth weight, gestational age, mother's age at birth of the child, and 1- and 5-min Apgar scores were included in the multivariable models. Calendar year at first FS was also included in adjusted models to evaluate for potential period effect.

2.4. Outcomes of interest

Three outcomes were evaluated in this study; one was associated with the index FS event (inpatient admission for FS), and the other two were subsequent to the index FS episode (recurrent FS and diagnosis of epilepsy). Inpatient admission for index FS was defined as admission on the same day or on the next day following occurrence. Recurrent FS was defined as a second FS event that occurred greater than 7 days following the index FS. A child could experience multiple recurrent events if each was separated by more than 7 days. Diagnosis of epilepsy was defined by ICD-9 codes 345.XX documented in the inpatient, outpatient and ED files following the index FS [22]. To evaluate the probability that ICD-9 FS codes documented on different dates (i.e. definition of recurrence) represented unique events rather than follow-up visits for a preceding event, a chart review was conducted ($n = 96$, 9%, of 1074 recurrent diagnosis dates) for patients with at least one recurrent FS, selected randomly with weighted sampling based on time interval between FS (shorter time interval, higher weight).

2.5. Statistical analyses

Unadjusted analyses were conducted to assess crude associations between VA versus NVA exposure and the outcomes of interest. Subsequently, four separate models were developed to assess adjusted risk for: inpatient admission for index FS, ever recurrence, counts of recurrence, and diagnosis of epilepsy. Inpatient admission was modeled as a binary outcome, and because 8% of patients were admitted for their first FS, we considered admission to be a common outcome and therefore fitted a Robust Poisson regression model [23]. Recurrence was modeled in two ways. First, time to first recurrence was evaluated using a Cox proportional hazards model. Second, a Robust Poisson model was used to estimate the relative rate of mean recurrence in which the FS variable was defined as a count of recurrences (range 0–9). Time to first epilepsy diagnosis was modeled using Cox proportional hazards model. Kaplan–Meier plots of recurrence ever and diagnosis of epilepsy were generated to check the proportional hazards assumption and to compare the survival distribution between VA and NVA groups. We presented the Kaplan–Meier plot as cumulative incidence (1 – Kaplan–Meier) in Fig. 1.

Adjusted analyses included the covariates mentioned above in all models, except for the inpatient admission model, which did not include the 1-min Apgar score due to near zero counts in some categories. We assessed for interactions between the VA versus NVA exposure and all other covariates in the model; evidence of interaction effect was determined by p-value <0.05 for type III test. Only one interaction term was added per iteration of the model.

With a type I error of 0.05, our post hoc power calculations demonstrated 85% power to detect a relative risk of 1.6 for inpatient admission outcome, 76% power to detect a relative risk of 1.3 for FC recurrence ever outcome, and 77% power to detect a relative risk of 1.8 for epilepsy outcome, between those who had vaccine-related 1st FS and non-vaccine-related 1st FS subjects given the observed groups sample size.