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Original Article

Risk of Subsequent Asthma in Children With Febrile Seizures: A Nationwide Population-Based Retrospective Cohort Study

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ABSTRACT

BACKGROUND: No study has reported a relationship between febrile seizures and asthma; thus, we examined the association between these two disorders. **METHODS:** We identified 991 cases of children with febrile seizures as the case cohort, and the control group was matched according to age, sex, urbanization level, and their parents' occupation at a 1:4 ratio. We applied the Cox proportional hazards regression model to estimate the hazard ratios and 95% confidence intervals for asthma among the children with febrile seizures. **RESULTS:** After 11 years of follow-up, the asthma incidence in the febrile seizure group was approximately 5% higher than that in the control group (log-rank test, $P < 0.0001$). The risk of asthma in the febrile seizure group was 1.41 times higher than that in the control group (95% confidence interval, 1.21-1.65; $P < 0.001$). Furthermore, the risk of asthma development increased (0.96 vs 3.62) in conjunction with the frequency of febrile seizure-related medical visits (one to two visits vs more than four visits; $P < 0.0001$). **CONCLUSION:** Febrile seizures may be associated with an increase in the risk of future asthma occurrence in children. We observed a significantly higher cumulative incidence of asthma occurrence in children with more febrile seizure-related medical visits.

Keywords: febrile seizure, asthma, nationwide population-based, cohort study

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Introduction

Febrile seizures are the most common type of seizure in humans.[1] Febrile seizures occur in 2-5% of children. They typically affect children aged 2 months to 5 years, and the incidence is identical in boys and girls.[2]

Proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, cause fever during infection. These cytokines not only play a role in activating an immune response after infection, but they also serve neuromodulatory functions and contribute to aberrant neuronal excitability underlying seizure disorders.[3] Numerous previous studies have reported an increased level of proinflammatory cytokines (including IL-1β and IL-6) in children with febrile seizures.[2,4-10] Specific viral infections have also been associated with febrile seizures, including human herpes virus (HHV)-6, influenza, adenovirus, respiratory syncytial virus (RSV), herpes simplex virus

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What is new in this subject

(1) Febrile seizures are associated with an increased risk of future asthma in children.
(2) Cumulative incidence of asthma is significantly higher in children with more febrile seizure-related medical visits.

(HSV)-1, and cytomegalovirus.[11] These fever-related inflammatory cytokines and specific viral infections have been postulated to contribute to the pathogenesis of febrile seizures.

Previous studies have reported an increasing incidence of atopic diseases such as asthma, particularly among children.[12,13] Researchers have focused on identifying multiple risk factors that cause the development of atopic diseases. Certain studies have reported elevated IL-6 and IL-1β levels in patients with asthma,[14-16] as well as increased expression of IL-1β on the asthmatic bronchial epithelium,[17,18] indicating that these cytokines might be involved in mediating both the proinflammatory processes and airway hyperresponsiveness that underlie asthmatic diseases. Several studies have reported that RSV and HSV-1 infection have an increased association with subsequent asthma development.[19-21] Both febrile seizures and asthma are common disorders among children, and they share a similar association with certain viral infections and proinflammatory cytokines. Thus, the objective of this study was to determine whether an increased risk of asthma exists among children with febrile seizures.

Method and Materials

The Taiwan National Health Insurance program is a unique program that was established by the Bureau of National Health Insurance on March 1, 1995. The program provides health insurance coverage for approximately 99% of the population of Taiwan.[22] The National Health Research Institutes maintains the National Health Insurance Research Database (NHIRD) of medical claims data. We obtained data from the Longitudinal Health Insurance Database 2000, a subset of the NHIRD, comprising data on one million insurants who were randomly selected from the original registry of insurants in 2000. The Longitudinal Health Insurance Database 2000 contains all medical records from 1996-2010, and the diseases were defined based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

We collected data on 1353 children (aged 1 month to 5 years) with newly diagnosed febrile seizures (ICD-9-CM 180.3) during the 2000-2005 period. We excluded data for 362 cases of children with epilepsy or recurrent seizures, myoclonus, seizures in newborn infants, or children with a history of asthma. The febrile seizure cohort comprised data on 991 children, and the date of febrile seizure diagnosis was set as the index date. Control patients were selected from children who were not diagnosed with febrile seizure before 5 years of age, and they were frequency matched at a 4:1 ratio based on age, sex, urbanization level, and their parents' occupations. The urbanization levels were categorized from Level 1 (highest level of urbanization) to Level 5 (lowest level of urbanization).[23] The follow-up period for all patients was from the index date to either the date of asthma diagnosis (ICD-9-CM 493) or the end of 2010.

The differences in demographics and comorbidities between the 2 groups were analyzed using the chi-square test for categorical variables and the *t* test for continuous variables. The comorbidities analyzed were allergic conjunctivitis (ICD-9-CM 372.05, 372.10, and 372.14), allergic rhinitis (ICD-9-CM 477), and atopic dermatitis (ICD9-CM 691.8), all of which were defined before the index date. Person-years were counted from the index date to asthma development, and the incidence of asthma per 1000 person-years was also calculated for both groups. The hazard ratio for asthma was assessed in comparison with the control group, and after controlling for comorbidity in the adjusted model, we observed statistically significant differences in comparison with the univariate model. We also estimated the association between asthma and the frequency of febrile seizure-related medical visits within the year after the index date. We used the Kaplan-Meier estimator to plot the proportion asthma free, and the log-rank test was used to test the differences between the two groups. All statistical analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC). All tests were two-tailed, and the level of statistical significance was set at 0.05.

Results

The febrile seizure and control groups comprised 991 and 3964 children, respectively. The mean age of the children with febrile seizures was 2.3 years (standard deviation, 1.20). Most of the children with febrile seizures were boys (56.8%), lived in urban areas (74.7% vs 25.3%), and had parents who worked in white collar positions (59.3% vs 40.7%). Compared with the control group, the children with febrile seizures exhibited a significantly higher frequency of comorbid conditions, including allergic conjunctivitis ($P = 0.002$) and allergic rhinitis ($P = 0.0001$; Table 1).

The incidence of asthma for the febrile seizure and control groups was 28.62 and 19.56 per 1000 person-years, respectively (Table 2). After 11 years of follow-up, the proportion of asthma-free patients in the febrile seizure group was approximately 5% lower than that in the control group (log-rank, $P < 0.0001$, Figure). The incidence of asthma in the febrile seizure group was higher among children aged 0.5 to 2.0 years (compared with those >2 years), boys, and

TABLE 1.
Demographics of Children with and Without Febrile Seizures

Variable	Febrile Seizures				*P* Value
	Yes (N = 991)		No (N = 3964)		
	n	%	n	%	
Age					>0.99
1 mo-2 years	476	48.0	1904	48.0	
2.1-5 years	515	52.0	2060	52.0	
Mean (SD)	2.30	(1.20)	2.33	(1.19)	0.55
Sex					>0.99
Boy	563	56.8	2252	56.8	
Girl	428	43.2	1712	43.2	
Urbanization					>0.99
1 (highest)	255	25.7	1020	25.7	
2	282	28.5	1128	28.5	
3	203	20.5	812	20.5	
4	149	15.0	596	15.0	
5 (lowest)	102	10.3	408	10.3	
Occupation					>0.99
White collar	588	59.3	2352	59.3	
Blue collar	268	27.0	1072	27.0	
Others	135	13.6	540	13.6	
Comorbidity					
Allergic conjunctivitis	66	6.86	171	4.31	0.002
Allergic rhinitis	109	11.0	288	7.27	0.0001
Atopic dermatitis	26	2.62	76	1.92	0.16

Abbreviation:
SD = Standard deviation
Chi-square test and *t* test.