



Original Article

Increased Association Between Febrile Convulsion and Allergic Rhinitis in Children: A Nationwide Population-Based Retrospective Cohort Study

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ABSTRACT

BACKGROUND AND OBJECTIVES: Febrile convulsions and allergic rhinitis are both common childhood disorders and both are considered as generally benign disorders. Yet, especially in the case of allergic rhinitis, adverse effects on school performance and limited socialization are found. The relationship between febrile convulsions and allergic rhinitis has not been previously reported; thus, this article seeks to explore the association between these two disorders by collecting data from the Taiwanese nationwide cohort database. **METHODS:** A total of 1304 children with febrile convulsions were identified as the case cohort, and controls were matched based on age, sex, urbanization levels, and parents' occupation on a 1 to 4 ratio. Cox's proportional hazards regression model was used to estimate the hazard ratio and confidence interval of allergic rhinitis disorder among children with febrile convulsions. **RESULTS:** During an average 6.7 years follow-up period, the incidence of allergic rhinitis in the febrile convulsions case group was higher (65.16 vs 51.45 per 1000 person-years). After 11 years of follow-up, the allergic rhinitis incidence in the febrile convulsion patients was approximate 4% higher than controls (log-rank test $P < 0.0001$). Risk of allergic rhinitis in the febrile convulsions group was found to be 1.21 times higher than in the control group (95% confidence interval, 1.08–1.36). This risk of allergic rhinitis development is further increased (0.94 vs 18.9) with frequency of febrile convulsions–related medical visits (one to three visits vs more than three visits, $P < 0.0001$). **CONCLUSION:** Febrile convulsions may be associated with allergic rhinitis occurrence in children. Children with more than three febrile convulsion–related medical visits had a significantly higher cumulative incidence of allergic rhinitis. Both disorders have previously been reported to have similar cytokine profiles and specific viral infection association. More studies are required to explore a possible link between the two disorders.

Keywords: febrile convulsion, allergic rhinitis, interleukin-1b, atopy

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Introduction

Febrile convulsions (FC) are caused by fever and considered to be the most common form of seizures in humans.¹ FC are exclusively limited to children, occurring in 2% to 5% of children, ages between 2 months and 5 years, and with equal incidence between boys and girls.²

Fever is induced by proinflammatory cytokines including interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α during infections. In addition to their involvement in

activating an immune response after infection, these proinflammatory cytokines also serve neuromodulatory functions and contribute to aberrant neuronal excitability underlying seizures.³ Various articles have also reported an increased level of proinflammatory cytokines, including IL-1 β and IL-6 in children with FC.^{2,4–10} Specific viral infections have also been associated with FC including those of human herpesvirus (HHV)-6, influenza, adenovirus, respiratory syncytial virus, herpes simplex virus-1 (HSV-1) and cytomegalovirus.¹¹ Thus, the generation of fever-related inflammatory cytokines and association with specific viral infections have been postulated to contribute to FC pathogenesis.

Increasing incidence of atopic diseases including allergic rhinitis has been reported over the past several decades, particularly among children, for largely unknown reasons.^{12,13} Particular focus has been on identifying multiple risk factors for development and progression of atopic diseases. Certain studies have demonstrated increased production of IL-1, TNF- α , and IL-6 in allergic rhinitis, with these proinflammatory cytokines contributing to the acute-phase response of inflammatory and immune diseases.^{14–17} With specific regard to allergic rhinitis and atopy, increased association with specific viral infections including HSV-I, rhinovirus, hepatitis B, and cytomegalovirus have also been reported.^{18–21} FC and allergic rhinitis are both common disorders among children, and according to previous literature, seem to share similar association with certain viral infections and proinflammatory cytokines. Thus this study seeks to determine if there is indeed an association between children with FC and allergic rhinitis.

Materials and Methods

Data source

The Taiwan National Health Insurance program was established on March 1, 1995, by the Bureau of National Health Insurance. More than 99% of the Taiwanese population is enrolled into this program at this time. The National Health Research Institutes was commissioned to construct National Health Insurance Research Databases (NHIRDs) for research proposals. The identification codes of beneficiaries were scrambled by a computer.

In this study, we used the Longitudinal Health Insurance Database, which is a subdataset of NHIRDs and contains 1 million beneficiaries randomly selected from those enrolled in the insurance program in 2000. The Longitudinal Health Insurance Database contained insurant information, outpatient and inpatient visits, and medical treatment records between January 1, 1996, and December 31, 2010. To define disease in the Longitudinal Health Insurance Database, the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM), codes were used. Based on the Personal Information Protection Act, this study was approved by the Institutional Review Board of the China Medical University.

Study subjects

A total of 1304 children with FC (ICD-9-CM 780.3) at 0.5 to 5 years old were collected in this study and the date of diagnosed seizures was set as entry date. We excluded 388 children with epilepsy and recurrent seizures (ICD-9-CM 209), myoclonus (ICD-9 code 333.2), convulsions in newborns (ICD-9 code 779.0), or allergic rhinitis (ICD-9-CM 477) history before the entry date. To minimize the influence of possible “reverse causation” owing to the allergic rhinitis before FC, we excluded those children with diagnosis of allergic rhinitis before the diagnosis of FC. Controls were selected from 0.5- to 5-year-old children without FC history in a 4 to 1 ratio. The control group was frequency-matched with age, sex, urbanization level, parent's occupation, and entry-year as the case group.

The exclusion criteria in control group were the same as with the case group. All study subjects were followed from the entry date to the first event, which was occurrence of allergic rhinitis up to the end of 2010.

Statistical analysis

All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC) and the significance level was set at a two-sided *P* value of less than 0.05. To test the differences of categorical and continuous variables between the two groups, chi-square and *t* tests were used. The categorical variables included sex, urbanization level, parents' occupation, and comorbidities. The urbanization levels were grouped into seven levels based on Liu's report.²² Because there were few people at urbanization levels 6 and 7, these were combined into level 5. Level 1 was the highest urbanized and the level 5 was the lowest. Parents' occupations were grouped into white, blue collar, and others. “Others” included retained, low income, clergy, and so forth. Comorbidities included diseases such as allergic conjunctivitis (ICD-9-CM 372.05, 372.10 and 372.14), asthma (ICD-9-CM 493), and atopic dermatitis (ICD-9-CM 691.8) and were defined before the entry date.

The incidence of allergic rhinitis was calculated as occurrence of allergic rhinitis divided by 1000 person-years during the study period. Cox proportional hazard regression was used to estimate the risk of FC-associated allergic rhinitis after controlling allergic conjunctivitis and asthma, which showed significant difference between the two groups. We also assessed the association between the frequency for FC-related medical visits per year and allergic rhinitis incidence. The frequency of medical visits was stratified by first quartile. Kaplan-Meier analysis was used to plot the cumulative incidence and log-rank analysis was used to test the difference of cumulative incidence between two groups.

Results

A total of 4580 children were selected in this cohort study: 916 and 3664 children as the FC case and control groups, respectively. The mean age in FC case group was 2.35 years of age (standard deviation = 1.13). Children in the FC case group were predominantly girls, lived in higher urbanized areas, and the parents' occupation was predominantly white collar. Compared with controls, FC patients were more likely to have associated comorbidities with allergic conjunctivitis and asthma (*P* < 0.05, [Table 1](#)).

During the average 6.7 year follow-up period, the incidence of allergic rhinitis in the FC case group was higher (65.16 vs 51.45 per 1000 person-years, [Table 2](#)). After 11 years of follow-up, the allergic rhinitis incidence in patients was approximate 4% higher than in controls (log-rank test *P* < 0.0001, [Figure](#)). The risk was 1.21-fold in the case group compared with the control group in the adjusted Cox proportional hazard model. The risk of younger children (0.5 to 2 years old) of developing allergic rhinitis was higher than those who were older (2.1 to 5 years old) (57.08 vs 51.25 per 1000 person-years). Age-specific risk in patients was approximately 20% significantly higher than controls. Boys were more prone to developing allergic rhinitis than girls (60.59 vs 45.55 per 1000 person-years). Children who lived in urbanized areas and children of parents with a white collar occupation had the highest allergic rhinitis incidence. In addition, compared with controls, patients with FS had a significantly higher risk of allergic rhinitis if they had parents with white collar jobs.

[Table 3](#) shows the association between the frequency for annual medical visits for FC and allergic rhinitis. Compared with controls, the risk increased by frequency from 0.94 (one to three FC-related visits) to 18.9 (more than three FC-related visits) (*P* < 0.0001). The risk trend for both female and male is identical.

TABLE 1.
Demographics between children with febrile convulsions and control

	Control (n = 3664)		Febrile Convulsions (n = 916)		P Value
	n	%	n	%	
Age, yr					1.00
0.5–2	1720	46.9	430	46.9	
2.1–5	1944	53.1	486	53.1	
Mean (standard deviation)	2.36	(1.15)	2.35	(1.13)	0.86
Sex					1.00
Boy	1532	41.8	383	41.8	
Girl	2132	58.2	533	58.2	
Urbanization					1.00
1 (highest)	892	24.3	223	24.3	
2	1040	28.4	260	28.4	
3	740	20.2	185	20.2	
4	576	15.7	144	15.7	
5 (lowest)	416	11.4	104	11.4	
Occupation					1.00
White collar	2108	57.5	527	57.5	
Blue collar	1060	28.9	265	28.9	
Others	496	13.5	124	13.5	
Comorbidity					
Allergic conjunctivitis	161	4.39	64	6.99	0.001
Asthma	206	5.62	74	8.08	0.006
Atopic dermatitis	77	2.10	24	2.62	0.34

Chi-square test and *t* test.

Discussion

This study found an increased association of allergic rhinitis (1.21-fold risk) among children with FC, with the risk to be significantly higher in children from 0.5 to 2 years

of age, of male sex, in the highest urbanization, and with parents with a white collar occupation. Irrespective of sex, risk of allergic rhinitis was found to increase exponentially with frequency of FC-related medical visits, with risk reaching as high as 18.9 in children with more than three medical visits. In addition, children with FC had a higher association with other atopic comorbidities, including asthma (8.08% vs 5.62%, $P = 0.006$) and allergic conjunctivitis (6.99% vs 4.39%, $P = 0.001$).

FC is associated with fever and infection.^{2–5,23} To ensure accuracy of the data collected, only children with diagnostic codes (including allergic rhinitis) appearing on at least three medical visits were recruited.

Mechanisms of viral infections in FS are multifaceted including fever itself, height of fever exceeding individual threshold of convulsive temperature, elevated cytokine response to infection, and the neurotropic nature of specific viruses.²³ Infection and fever cause increased levels of proinflammatory cytokines in the periphery and the brain, thus precipitating seizure events.³ The study by Choi et al. has demonstrated higher serum levels of high mobility group box-1, IL-6, and IL-1 β in FS patients than in fever-only controls ($P < 0.05$), thus suggesting causative role of proinflammatory cytokine network in FC generation.⁴ In another study of double-stranded RNA-stimulated leukocytes in FS by Matsuo et al.,⁵ greater numbers of IL-6 and IL-10 were found in FC patients than in control after 24 hours of lipopolysaccharide stimulation. In addition, increased IL-1 β production from double-stranded RNA-stimulated leukocytes in children with FC was also found.⁵ Potential mechanisms of these proinflammatory cytokines, especially IL-1 β , involve both excitatory (glutamatergic) and inhibitory (GABAergic) systems. IL-1 β has been shown to alter N-methyl-D-aspartate receptor

TABLE 2.
The risk of allergic rhinitis versus children without febrile convulsions stratified by demographics in Cox proportional hazard regression

	Control			Febrile Convulsions			HR (95% CI)
	Event No.	Person-Years	IR	Event No.	Person-Years	IR	
All	1284	24,955	51.45	380	5831	65.16	1.21 (1.08–1.36) [†]
Age, yr							
0.5–2	652	11,971	54.47	191	2797	68.29	1.19 (1.01–1.40)*
2.1–5	632	12,984	48.68	189	3035	62.28	1.23 (1.04–1.44)*
Sex							
Boy	813	14,105	57.64	241	2542	73.26	1.22 (1.05–1.41) [†]
Girl	471	10,850	43.41	139	3290	54.68	1.21 (1.00–1.47)*
Urbanization							
1 (highest)	364	5743	63.38	107	1315	81.28	1.22 (0.99–1.52)
2	366	7117	51.43	116	1592	72.86	1.33 (1.07–1.64) [†]
3	247	5074	48.68	72	1244	57.88	1.16 (0.89–1.50)
4	184	3938	46.73	54	904	59.75	1.24 (0.91–1.67)
5 (lowest)	123	3083	39.90	31	775	39.99	1.04 (0.70–1.54)
Occupation							
White collar	815	13,703	59.48	253	3134	80.73	1.29 (1.12–1.49) [†]
Blue collar	326	7742	42.11	87	133	47.46	1.08 (0.85–1.37)
Others	143	3509	40.75	40	864	46.28	1.11 (0.78–1.57)

Abbreviations:

CI = Confidence interval

HR = Hazard ratio

IR = Incidence rate, per 1000 person-years

Model adjusted for allergic conjunctivitis and asthma.

* $P < 0.05$.† $P < 0.01$.‡ $P < 0.001$.

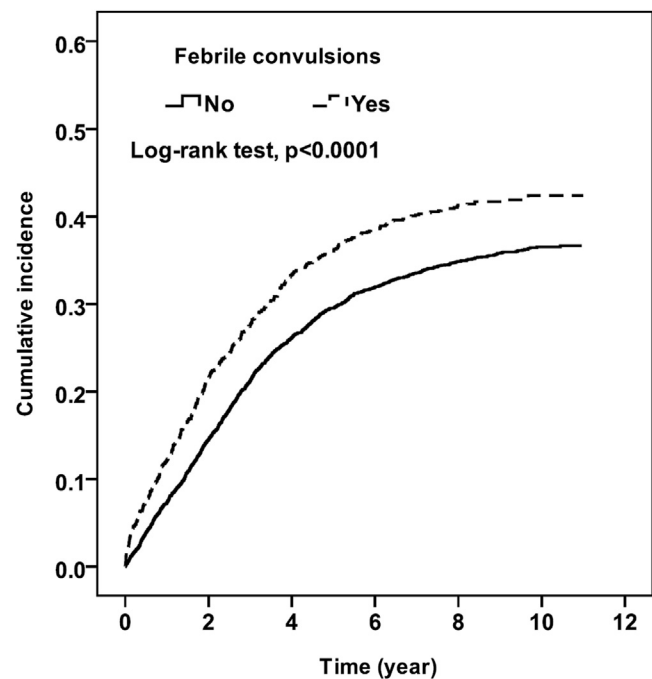


FIGURE.
The Kaplan-Meier estimated cumulative incidence of allergic disease.

phosphorylation, thus increasing excitatory neurotransmission with resultant seizure.^{2,24,25} There is also evidence that IL-1 β can affect GABAergic inhibition.^{2,26,27} Similar proinflammatory cytokine profiles have also been found in patients with allergic rhinitis.^{15–18} Allergic response is composed of both early and late reactions. The early reaction is mediated by mast cells and the release of preformed biochemical mediators (histamine, tryptase) and other rapidly generated mediators of inflammation (leukotrienes, prostaglandins). The late reaction involves the production of newly synthesized mast cell mediators and activation of inflammatory cells such as T-helper cells, eosinophils, basophils, and others. Accompanying this late reaction is the release of multiple cytokines including IL-1 β , IL-5, IL-6, IL-8, TNF- α , and macrophage inflammatory protein-1 α .^{16–18} This is reiterated in the study by Bensch et al. in which significantly increased peak levels of TNF- α , IL4, IL-10, and macrophage

inflammatory protein-1 α have been found after allergen challenge.¹⁶ This similarity in the cytokine profile between FC and allergic rhinitis could explain increased risk association between the two disorders found in this study.

Both FC and allergic rhinitis have also been reported with specific viral infections. In an Italian series by Bertolani et al. in children with mean age of 18 months, the incidence of viral infection in FS was HHV-6 (35%), adenovirus (13.8%), respiratory syncytial virus (10.7%), HSV-1 (9.2%), cytomegalovirus (3%), and HHV-7 (2.3%).¹¹ Review of HHV-6 infection and febrile seizures has shown varied results, with literature review demonstrating variability from 8% to 100% occurrence of seizure in HHV-6–infected children.²³ This demonstrates that the virus is not the only etiological factor. Fever associated with HHV-6 was found to be higher in those with seizures (39.93°C vs 39.68°C, $P = 0.048$) in study by Jee et al.,²⁸ and because fevers are regulated by proinflammatory cytokines released during viral infection, this again emphasizes the link between viral infection, fever, and FC. Viral disease during childhood and adolescence contributes to the development of allergic rhinitis, with increased rates of sensitization to aeroallergens (odds ratio 1.394, 95% confidence interval 1.128–1.723, $P = 0.0021$).²⁹ Studies have also demonstrated association between HSV-1 infection and atopy,^{30,31} with significantly higher HSV-1 IgG seropositivity found in atopic children (56.8%) with allergic rhinitis and asthma than in age-matched nonatopic children (30.4%) ($P < 0.001$).¹⁸

Limitations

The strengths of our study include its use of population-based data that are highly representative of the general population. However, certain limitations to our findings should be considered. First, the NHIRD does not contain detailed information regarding socioeconomic status and family history of systemic diseases, all of which may be risk factors for FC or allergic rhinitis. Second, the evidence derived from a retrospective cohort study is generally lower in statistical quality than that from randomized trials because of potential biases related to adjustments for confounding variables. Despite our meticulous study design and control measures for confounding factors, bias resulting from unknown confounders may have affected our results.

TABLE 3.
The risk of allergic rhinitis among frequency of medical visits of febrile convulsions in cox proportional hazard regression

Frequency of FC Medical Visit, per Year	All			Female			Male		
	Event No.	IR	HR (95% CI)	Event No.	IR	HR (95% CI)	Event No.	IR	HR (95% CI)
All									
None	1284	51.45	1.00	471	43.41	1.00	813	57.64	1.00
1–3	289	50.1	0.94 (0.82–1.06)	112	44.43	0.99 (0.81–1.22)	177	54.51	0.91 (0.77–1.07)
>3	91	1433	18.9 (15.2–23.6)†	27	1280	19.4 (13.0–29.1)†	64	1510	18.3 (14.0–23.9)*
P for trend			<0.0001			0.001			<0.0001

Abbreviations:
CI = Confidence interval
FC = Febrile convulsions
HR = Hazard ratio
IR = Incidence rate, per 1000 person-years
Model adjusted for allergic conjunctivitis and asthma.
* $P < 0.001$.

Third, all data in the NHIRD are anonymous; thus, relevant clinical variables, such as blood pressure, imaging results, pathology findings, and serum laboratory data were unavailable regarding our study patients. However, the data regarding the diagnoses of febrile convulsion or allergic rhinitis were nonetheless reliable.

Conclusion

Findings in this study included increased association of allergic rhinitis in children with FC, with exponentially increasing allergic rhinitis risk in children with multiple FC-related medical visits. The seizure pathogenesis in FC and immune mechanisms in allergic rhinitis is extremely complicated, and etiology of both disorders is multifactorial, but there may be a yet-unidentified common link. This study has demonstrated a significant association in children with FC and allergic rhinitis; possible mechanisms postulated include exposure to specific viral infections and the sharing of similar proinflammatory cytokine profiles. Yet much work is still needed to fully explain the exact mechanisms and associations between these two disorders.

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