의학석사 학위논문

Longitudinal analysis of risk factors of febrile seizures and future risk of epileptic seizure based on the national sample cohort in South Korea, 2002-2013

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지도교수 곽 영 호

이 논문을 의학석사 학위논문으로 제출함

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서울대학교 대학원

의학과 응급의학전공

최 유 진

최 유 진의 석사 학위논문을 인준함

2019년 7월

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Abstract

Longitudinal analysis of risk factors of febrile seizures and future risk of epileptic seizure based on the national sample cohort in South Korea, 2002 - 2013

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Introduction: Febrile seizure is a relatively common disease that affects approximately 2 - .5% of children between the ages of three months and five years. We performed a large, population-based study to analyze the risk factors of the febrile seizures and the subsequent epileptic seizures.

Methods: Relevant data from children born between 2002 - .2007 were retrieved from the Korean National Health Insurance Service-National Sample Cohort 2002-2013. Children who did not survive the first five years were excluded from the analysis. The risk factors for febrile seizures were assessed separately in per-person and perfebrile case analyses, and factors contributing

to an increased risk of subsequent epileptic seizures were identified.

Results: A total of 54,233 children were included and the five-year prevalence rate of febrile seizure was 11.19%. In the per-person analysis, male sex, preterm birth and brain injury at birth increased the risk of febrile seizure with odds ratios of 1.17, 1.40 and 1.97 (all $p < 0.001$), respectively. A high household income level was associated with reduced odds of febrile seizure. In the per-febrile illness analysis, male sex, brain injury at birth, presumed bacterial infection, gastrointestinal or genitourinary infection and unspecified sepsis were independent risk factors of a febrile seizure during febrile illness. The cumulative number of febrile seizure episodes, especially more than the third episodes, was associated with a new diagnosis of an epileptic seizure within one year.

Conclusions: Sex, preterm birth, brain injury at birth, presumed bacterial infection, genitourinary and gastrointestinal infections and unspecified sepsis were identified as likely risk factors for febrile seizures. A greater number of febrile seizure episodes was associated with a higher probability of subsequent epileptic seizures.

Keywords : Febrile seizure, epileptic seizure, risk factor
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Contents

List of tables and figures

Introduction

Febrile seizure is a relatively common complication of fever that affects approximately 2 – 5% of children between the ages of three months and five years[1]. The incidence of febrile seizures varies geographically according to several studies, with incidence rates of 9.3% in Japan, 14% in Guam and 10% in India[2,3,4]. However, most previous studies were based on snapshot data from regional populations or hospital visits, and few population-based studies used longitudinal analysis from birth, especially in Korea[5,6,7,8].

Febrile seizure is widely believed to be mostly benign; however, this belief has been questioned recently. A total of 6% of children who visited the pediatric emergency departments of four hospitals with their first febrile seizure had an unprovoked seizure within the following two years[9].Additionally, a population study based on the Danish national cohort reported that the cumulative incidence of epilepsy following febrile seizure was 6.9% at 23 years of follow-up, which was a higher rate than that of children without febrile seizures[7].

Based on previous findings, we constructed two hypotheses. The first is that febrile seizures occur most preferentially in patients with underlying conditions and severe forms of febrile illness, such as bacterial infections. The second is that febrile seizure, especially if it is recurrent, is a significant risk factor for future epileptic seizures. Because we thought that these hypotheses should be verified in a cohort of children with full longitudinal information, we constructed a cohort dataset of children using a nationally representative claim database.

Therefore, the purpose of this study was twofold. The primary objective was to analyze the risk factors of febrile seizures and determine whether the underlying conditions and characteristics of febrile illnesses were associated with the risk factors. The secondary objective was to assess the risk of newly diagnosed epileptic seizures after febrile seizures.

Materials and Methods

Data source

The data source was the National Health Insurance Service-National Sample Cohort (NHIS-NSC) 2002-2013, which includes information for approximately 1 million people, comprising 2.2% of the total eligible population in South Korea. This cohort consists of randomly selected samples that are stratified with proportional allocation according to age, sex, region, health insurance type and household income. Each dataset is labeled with a unique, anonymous identification number for each patient and includes the patient's age, sex, type of insurance, a list of diagnoses according to the International Classification of diseases, tenth revision (ICD-10), medical costs claimed, prescribed medication and treatments covered by the National Health Insurance and hospital facility information. The cohort population is refreshed annually by adding a representative sample of newborns from each year because preexisting patients' eligibilities are disqualified by death or immigration[10]. This study was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No: X-170/ 411-901).

Study population

The inclusion criterion was children born from 2002-2007 who had complete information available for at least six years after birth. We scanned every febrile seizure episode from birth until the age of five years and used the last year for analysis of subsequent epileptic seizures. The decision regarding the limited observation time window was made a priori to maximize inclusion. The decision was also based on previous reports of a low incidence rate of febrile seizures after five years of age[1]. Children who did not survive the first five years were excluded. The ages of the children are based on their birth years, because the cohort dataset provides only the year of birth and does not include the exact birthdate of the enrollees. Consequently, the age 0 is defined for children with the same year of birth and age 1 as the next year.

Analytical schemes and definitions

The risk factors for febrile seizures were assessed using two different methods. The first method was a per-person analysis in which sex, perinatal problems and the household income level at birth as well as any occurrence of febrile seizure (ICD-10 code R56.0x) and epileptic seizure (ICD-10 code G40.x or G41.x) were analyzed. This ICD - 10 code based disease definition in this claim data is dependent on the physicians' clinical judgement. We assume that their decisions were made according to the international definition of febrile seizure which occurs in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of epilepsy. And also we assume that they considered a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain as epileptic seizure.

The presence of a perinatal problem was defined as ICD-10 code P07.0x or P07.1x for low birth weight, P07.2x or P07.3x for preterm birth and P10.x, P11.x (except for P11.5 for birth injury to the spine and spinal cord), P52.x, P91.x or G80.x for birth-related brain injury or cerebral palsy. Birth related brain injury or cerebral palsy was described as 'Brain injury at birth' in our analysis which defined as outcomes of perinatal injuries of the CNS manifest as the result of the difficult delivery such as skull fracture, hemorrhage or hypoxic-ischemic event.

We defined the household income level into three categories as follows: low-income level (income level quantile $\leq$30% or recipients of a medical aid program), middle-income level (income level quantile >30% and $\leq$70) and high-income level (income level quantile >70%).

The second method was a per-febrile illness case analysis in which information specific to each febrile illness case, including the age of onset, presumed type of pathogen (bacterial vs. viral), site of infection, previous history of febrile seizure and epileptic seizure before the onset of the event, occurrence of a febrile seizure during the illness and general information for the enrolled children, including perinatal problems and the household income level assessed at the year of the event. We categorized presumed type of pathogen according to

each of ICD-10 codes before analysis; for instance, ICD-10 code A00 cholera as 'bacterial infection', B00 herpes simplex infections as 'viral infection', B86 scabies as 'fungal or parasite infection' and J01 acute sinusitis as 'unknown' and so on. And we only compared 'bacterial infection' and 'viral infection' between the groups because the 'fungal or parasite infection' was so minimal and 'unknown' was unclear for the pathogen categories.

A febrile illness case was defined as each outpatient or inpatient visit to a clinic or a hospital with a prescription/administration of antipyretics (ATC code N02) or a primary or secondary diagnosis of fever (ICD-10 code R50.x or R56.0x) without such a visit within one week prior to the index visit. We excluded central nervous system infections because of the febrile seizure definition[11]. The site of infection was classified as 1)respiratory, 2)sinus, 3)inner ear, 4)gastrointestinal, 5)genitourinary, 6)skin and soft tissue, 7)sepsis and 8)other sites or unspecified using a previously developed categorization system of ICD-10 codes according to infectious episode type[12]. Visits that were followed by an antipyretics prescription or a fever diagnosis within one week were considered the same visit as the febrile illness. The occurrence of febrile seizures during illness event was determined as an occurrence of an ICD-10 code for febrile seizure(R56.0x) during the index visit or subsequent visits. However, if a concomitant epileptic seizure diagnosis was made, the case was labeled an epileptic seizure instead of seizure.

The risk factors for a newly diagnosed epileptic seizure after a febrile seizure event, which was our secondary objective, were assessed by analyzing the febrile seizure event in patients without any prior history of epileptic seizure since birth. The total cumulative number of febrile seizure episodes (categorized as one, two, three, four and five or more), age, presumed pathogen, site of infection, history of perinatal problems and household income level assessed at the year of the event were analyzed.

Statistical analysis

Categorical variables were reported using frequencies and proportions, and continuous variables were reported using medians and interquartile ranges

(IQRs). Wilcoxon's rank-sum test, the chi-square test, or Fisher's exact test was performed as appropriate for between-group comparisons. We used multiple logistic regression for the per-person analysis to identify general risk factors for having a febrile seizure event during the first five years after birth. We used random-effects multiple logistic regression for the per-febrile illness case analysis to identify risk factors for an epileptic seizure diagnosis within one year after a febrile seizure. In this analysis, covariates were restricted to those with p-values less than 0.1 for the difference between the groups with and without an epileptic seizure diagnosis within 1 year after a febrile seizure event. The analysis results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value <0.05 was considered significant. All data handling and statistical analyses were performed using the R package version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1. Population characteristics

		Febrile seizure (n=6,074)	No febrile seizure (n=48,159)	p
Sex				<0.001
	Male	3,370 (55.48%)	24,787 (51.47%)	
	Female	2,704 (44.52%)	23,372 (48.53%)	
Age of onset*				
	0	527 (8.68%)		
	1	2,171 (35.74%)		
	2	1,578 (25.98%)	Not applicable	
	3	946 (15.57%)		
	4	517 (8.51%)		
	5	335 (5.52%)		
History of epileptic seizure before the first episode		248 (4.08%)	Not applicable	
Any epileptic seizure until age five		492 (8.10%)	615 (1.28%)	<0.001
Low birth weight		44 (0.72%)	247 (0.51%)	0.042
Preterm birth		73 (1.20%)	357 (0.74%)	<0.001
Brain injury at birth		80 (1.32%)	300 (0.62%)	<0.001
Household income level at birth				
	Low	814 (13.40%)	6,181 (12.83%)	0.002
	Middle	3,310 (54.49%)	25,432 (52.81%)	
	High	1,950 (32.10%)	16,546 (34.36%)	

*Age of onset was assessed based on the birth year. The age 0 is the same for all children with the same year of birth, and the age 1 indicates the next year.

A total of 54,293 newborns from 2002 to 2007 were identified from the NHIS-NSC dataset. After the exclusion of 60 newborns (0.11%) who did not survive the first five years, a total of 54,233 newborns were included and observed until the age of five years. Table 1 shows the per-person characteristics of the study population. A total of 6,074 children were diagnosed with at least one febrile seizure before the age of five years; thus, the five-year prevalence rate was 11.19%. In the affected population, the peak age of onset

was two years of age (35.74%) and the male sex was more predominant, with a rate of 55.48% compared to those unaffected (51.47%, $p<0.001$). The overall prevalence of epileptic seizure was significantly higher in the affected group (8.10% vs. 1.28%; $p<0.001$), and 4.08% of the affected population had a previous history of epileptic seizure before their first attack of febrile seizure. Histories of a low birth weight (0.72%), preterm birth (1.20%) and brain injury at birth (1.32%) were more prevalent in the affected than in the unaffected population (0.51%, 0.74% and 0.62%, respectively) with corresponding p-values of 0.042, <0.001 and <0.001, respectively. The household income levels of the affected population had a higher proportion of low-income levels at birth (13.40% vs. 12.83%, $p=0.002$) and a lower proportion of high-income levels at birth (32.10% vs. 34.36%, $p=0.002$).

Table 2. Multiple logistic regression model for febrile seizure until five years of age

	Odds ratio (95% confidence interval)	p
Sex, male	1.17 (1.11-1.24)	<0.001
Low birth weight	0.96 (0.65-1.41)	0.818
Preterm birth	1.40 (1.03-1.91)	0.034
Brain injury at birth	1.97 (1.52-2.55)	<0.001
Low income level	1.01 (0.93-1.10)	0.774
Mid income level	Reference	
High income level	0.90 (0.85-0.96)	0.001

After adjustment using multiple logistic regression (Table 2), the per-person risk factors for febrile seizure were a male sex, preterm birth and brain injury at birth, with respective ORs of 1.17 (95% CI, 1.11-1.24; p<0.001), 1.40(95% CI, 1.03-1.91; p=0.034) and 1.97(95% CI, 1.52-2.55; p<0.001). A high-income level was associated with a lower risk, with an OR of 0.90(95% CI, 0.85-0.96; p=0.001).

Table 3. Febrile illness cases with and without febrile seizure

	With febrile seizure (n=9,492)	Without febrile seizure (n=1,413,797)	p
Age, median (IQR)	2.0 (1.0-3.0)	3.0 (1.0-4.0)	<0.001
Sex			<0.001
Male	5,321 (56.06%)	745,482 (52.73%)	
Female	4,171 (43.94%)	668,315 (47.27%)	
Presumed pathogen			
Bacterial	972 (10.24%)	83,065 (5.88%)	<0.001
Viral	4,457 (46.96%)	718,091 (50.79%)	<0.001
Site/type of infection			
Respiratory	7,585 (79.91%)	1,207,558 (85.41%)	<0.001
Sinus	769 (8.10%)	201,836 (14.28%)	<0.001
Inner ear	839 (8.84%)	156,016 (11.04%)	<0.001
Gastrointestinal	1,858 (19.57%)	194,501 (13.76%)	<0.001
Genitourinary	267 (2.81%)	9,855 (0.70%)	<0.001
Skin and soft tissue	463 (4.88%)	76,928 (5.44%)	0.017
Sepsis	42 (0.44%)	1,216 (0.09%)	<0.001
Others and unspecified	1,533 (16.15%)	191,826 (13.57%)	<0.001
Number of previous febrile seizure episodes			<0.001
None	6,074 (63.99%)	1,384,982 (97.96%)	
1	1,672 (17.61%)	17,687 (1.25%)	
2	694 (7.31%)	5,568 (0.39%)	
3	368 (3.88%)	2,383 (0.17%)	
4	217 (2.29%)	1,413 (0.10%)	
5	467 (4.92%)	1,764 (0.12%)	
Previous history of any epileptic seizure	922 (9.71%)	21,696 (1.53%)	<0.001
Low birth weight	56 (0.59%)	7,389 (0.52%)	0.404
Preterm birth	106 (1.12%)	11,301 (0.80%)	0.001
Brain injury at birth	179 (1.89%)	9,553 (0.68%)	<0.001
Household income level (at the event)			<0.001
Low	1306 (13.76%)	171019 (12.10%)	

Middle	5147 (54.22%)	760143 (53.77%)	
High	3039 (32.02%)	482635 (34.14%)	
New epileptic seizure within one month*	123/8570 (1.44%)	462/1392101 (0.03%)	<0.001
New epileptic seizure within one year*	282/8570 (3.29%)	4509/1392101 (0.32%)	<0.001

* Among patients without a previous history of any epileptic seizure

Table 3 shows the clinical characteristics of each febrile illness episode for the 54,233 participants. The per-febrile illness case analysis results were expressed as frequencies, proportions and medians (IQRs). Febrile seizures were more frequently observed in febrile illnesses involving patients who were younger (age, median 2.0 vs. 3.0; IQR 1-3 vs. 1-4; $p<0.001$) and male (56.06% vs. 52.73%; $p<0.001$). Presumed bacterial infections were relatively more frequent in cases accompanied by febrile seizure (10.24% vs. 5.88%; $p<0.001$). Gastrointestinal (19.57% vs. 13.76%; $p<0.001$), genitourinary (2.81% vs. 0.70%; $p<0.001$) and unspecified sepsis (0.44% vs. 0.09%; $p<0.001$) were more frequent infection sites in patients with febrile seizure. Hospital visits for febrile seizure cases had a higher prevalence of previous histories of febrile seizures (36.0% vs. 2.0%, $p<0.001$) and epileptic seizures (9.7% vs. 1.5%; $p<0.001$) before the events than visits for febrile illness without febrile seizure. Histories of preterm birth (1.12% vs. 0.80%; $p=0.001$) and brain injury at birth (1.89% vs. 0.68%; $p<0.001$) were also significantly more frequent in the patients with febrile seizure. A similar shift was observed in the household income level toward a low-income level ($p<0.001$), as shown in the per-person analysis. Febrile seizure was associated with a significantly higher risk of a new diagnosis of epileptic seizure within one month (1.44% vs. 0.03%; $p<0.001$) and one year (3.29% vs. 0.32%; $p<0.001$).

Table 4. Random-effects multiple logistic regression model for febrile seizure during febrile illnesses

	Odds ratio (95% confidence interval)	p
Age, per year	0.64 (0.63-0.65)	<0.001
Sex, male	1.06 (1.02-1.11)	0.007
Presumed pathogen		
Bacterial	1.40 (1.29-1.52)	<0.001
Viral	0.88 (0.84-0.92)	<0.001
Site/type of infection		
Respiratory	0.67 (0.63-0.71)	<0.001
Sinus	0.51 (0.47-0.55)	<0.001
Inner ear	0.72 (0.67-0.77)	<0.001
Gastrointestinal	1.36 (1.28-1.43)	<0.001
Genitourinary	2.19 (1.89-2.54)	<0.001
Skin and soft tissue	0.72 (0.65-0.80)	<0.001
Sepsis	1.72 (1.24-2.39)	0.001
Others and unspecified	1.07 (1.01-1.13)	0.021
Number of previous febrile seizure episodes		
0	Reference	
1	29.54 (27.69-31.51)	<0.001
2	39.93 (36.30-43.93)	<0.001
3	48.93 (42.99-55.68)	<0.001
4	50.02 (42.39-59.03)	<0.001
5	70.58 (61.50-81.00)	<0.001
Previous history of any epileptic seizure	1.65 (1.50-1.81)	<0.001
Low birth weight	1.22 (0.88-1.68)	0.231
Preterm birth	1.22 (0.95-1.56)	0.114
Brain injury at birth or cerebral palsy	1.44 (1.19-1.73)	<0.001
Household income level		
Low	1.06 (0.99-1.13)	0.108
Middle	Reference	
High	0.95 (0.91-1.00)	0.043

Table 4 shows the random-effects multiple logistic regression results for every factor in Table 3. A younger age, male sex, presumed bacterial pathogen, gastrointestinal or genitourinary infection, sepsis, cumulative number of febrile seizure events, previous episodes of febrile seizure or epileptic seizure and brain injury at birth or cerebral palsy were independent risk factors of a febrile seizure during febrile illness. All of the specific odds ratios and p-values are

provided in the table.

Table 5 shows the characteristics of febrile seizure events by the cumulative number of episodes; the results are expressed as frequencies, proportions and medians (IQRs). More than one-fourth of the first febrile seizure events (1,672/6,074, 27.53%) were followed by a second event. In 11.26% (684/6,074) of the patients, more than five episodes of febrile seizure were observed during the first five years. A history of epileptic seizure prior to each episode and brain injury at birth were significantly associated with an increasing number of febrile seizure events (all $p<0.001$). The cumulative number of febrile seizure episodes was associated with a new diagnosis of epileptic seizure within one year ($p<0.001$).

Table 5. Characteristics of febrile seizure events by the number of cumulative episodes

	One (n=6074)	Two (n=1672)	Three (n=694)	Four (n=368)	Five or more (n=684)	p
Age, median (IQR)	2.0 (1.0-3.0)	2.0 (2.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (3.0-4.0)	<0.001
Sex						0.543
Male	3370 (55.48%)	949 (56.76%)	390 (56.20%)	213 (57.88%)	399 (58.33%)	
Female	2704 (44.52%)	723 (43.24%)	304 (43.80%)	155 (42.12%)	285 (41.67%)	
History of any epileptic seizure	248 (4.08%)	180 (10.77%)	118 (17.00%)	87 (23.64%)	289 (42.25%)	<0.001
Low birth weight	44 (0.72%)	8 (0.48%)	3 (0.43%)	1 (0.27%)	0 (0.00%)	0.125
Preterm birth	73 (1.20%)	19 (1.14%)	9 (1.30%)	4 (1.09%)	1 (0.15%)	0.168
Brain injury at birth	80 (1.32%)	31 (1.85%)	15 (2.16%)	11 (2.99%)	42 (6.14%)	<0.001
Household income level						0.976
Low	814 (13.40%)	237 (14.17%)	99 (14.27%)	55 (14.95%)	101 (14.77%)	
Middle	3310 (54.49%)	903 (54.01%)	371 (53.46%)	196 (53.26%)	367 (53.65%)	
High	1950 (32.10%)	532 (31.82%)	224 (32.28%)	117 (31.79%)	216 (31.58%)	
New epileptic seizure within one month*	76/5826 (1.30%)	24/1492 (1.61%)	6/576 (1.04%)	8/281 (2.85%)	9/395 (2.28%)	0.108
New epileptic seizure within one year*	158/5826 (2.71%)	57/1492 (3.82%)	26/576 (4.51%)	18/281 (6.41%)	23/395 (5.82%)	<0.001

*Among patients without a previous history of any epileptic seizure

The risk factors for epileptic seizure after a febrile seizure event were assessed in the febrile seizure cases without any previous or concomitant epileptic seizure diagnosis. The cumulative number of febrile seizure episodes ($p<0.001$), age ($p=0.048$) and a history of brain injury (2.48% vs. 0.65%; $p=0.001$) at birth were significantly associated with the risk of an epileptic seizure diagnosis within one year (Table 6).

Table 6. Febrile seizure episodes with and without new epileptic seizure diagnosis within a year

	Epileptic seizure in a year (N=282)	No epileptic seizure in a year (N=8288)	*p*
Cumulative number of febrile seizure episodes			<0.001
1	158 (56.03%)	5668 (68.39%)	
2	57 (20.21%)	1435 (17.31%)	
3	26 (9.22%)	550 (6.64%)	
4	18 (6.38%)	263 (3.17%)	
5	23 (8.16%)	372 (4.49%)	
Median age, (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.048
Sex			0.191
Male	147 (52.13%)	4661 (56.24%)	
Female	135 (47.87%)	3627 (43.76%)	
Presumed pathogen			
Bacterial	35 (12.41%)	871 (10.51%)	0.356
Viral	129 (45.74%)	3952 (47.68%)	0.562
Site/type of infection			
Respiratory	217 (76.95%)	6730 (81.20%)	0.086
Sinus	13 (4.61%)	667 (8.05%)	0.047
Inner ear	29 (10.28%)	731 (8.82%)	0.457
Gastrointestinal	53 (18.79%)	1655 (19.97%)	0.682
Genitourinary	10 (3.55%)	236 (2.85%)	0.610
Skin and soft tissue	14 (4.96%)	398 (4.80%)	1.000
Sepsis	1 (0.35%)	38 (0.46%)	1.000
Others and unspecified	55 (19.50%)	1354 (16.34%)	0.184
Low birth weight	1 (0.35%)	51 (0.62%)	0.869
Preterm birth	4 (1.42%)	88 (1.06%)	0.781
Brain injury at birth	7 (2.48%)	54 (0.65%)	0.001
Household income level			0.015
Low	29 (10.28%)	1169 (14.10%)	
Middle	143 (50.71%)	4509 (54.40%)	
High	110 (39.01%)	2610 (31.49%)	

Sex, the presumed pathogen and most types of infection (except for sinus infection, 4.61% vs 8.05%; p=0.047) did not show a significant association with the risk of an epileptic seizure diagnosis within one year. Household income levels at the time of the febrile seizure events showed a significant shift to a high-income level in patients with a new diagnosis of epileptic seizure (p=0.015).

Table 7. Random-effects multiple logistic regression model for epileptic seizure within one year after a febrile seizure episode

	Odds ratio (95% confidence interval)	p
Cumulative number of febrile seizure episodes: 1	Reference	
Cumulative number of febrile seizure episodes: 2	1.79 (0.98-3.30)	0.060
Cumulative number of febrile seizure episodes: 3	2.76 (1.20-6.33)	0.017
Cumulative number of febrile seizure episodes: 4	5.82 (2.08-16.26)	<0.001
Cumulative number of febrile seizure episodes: 5 or more	16.08 (5.60-46.20)	<0.001
Age, per 1 year	1.04 (0.82-1.32)	0.732
Respiratory infection	0.94 (0.51-1.73)	0.835
Sinus infection	0.53 (0.17-1.61)	0.265
Brain injury at birth or cerebral palsy	6.46 (0.59-70.28)	0.126
Low-income level	0.66 (0.22-1.96)	0.455
Mid-income level	Reference	
High-income level	1.27 (0.63-2.53)	0.506

Table 7 showed that the number of cumulative episodes was the only independent risk factor with a significant increase in the risk of subsequent epileptic seizures from the third episodes in the random-effects multiple logistic regression analysis (OR, 2.76, 5.82 and 16.08; 95% CI, 1.20-6.33, 2.08-16.26 and 5.60-46.20; p=0.017, <0.001 and <0.001, respectively, for a cumulative number of events of 3, 4 and).

Discussion

In this study, we tested two hypotheses. The first hypothesis was whether the risk of febrile seizure development was dependent on perinatal problems and the characteristics of febrile illness. The second hypothesis was whether febrile seizure was associated with future development of new epileptic seizures. We found that the susceptibility to febrile seizure was dependent on both perinatal problems, especially brain injury, and the characteristics of febrile illnesses, such as the causative pathogens and infection sites. We also found that febrile seizure was associated with an increased risk of epileptic seizure and that having multiple febrile seizure episodes (3 cumulative episodes) was an independent risk factor for a new diagnosis of epileptic seizure within one year.

In this study, the overall prevalence of febrile seizure in the first five years of the observation period was 11.19%, which was higher than the worldwide incidence (2-5%) and that of Japan (9.3%), which is located geographically close to South Korea[1,2].Byeon et al[8] reported that the prevalence of febrile seizure in Korean children younger than five years of age was 6.92% based on national cohort data, which was different from our result. We believe that this discrepancy is the result of the different inclusion criteria; we used R56.0x (febrile seizure) as an inclusion criterion, which has been used in many previous studies, whereas Byeon et al used R56.0x combined with G41.x (status epilepticus) or R56.8x (seizure)[7,13].

In this study, a male sex, preterm birth and brain injury at birth were independently associated with an increased risk of having febrile seizures in the per-person analysis. Similar to the reports of Vestergaard et al[7,14], these findings suggest that the susceptibility to febrile seizure is dependent on perinatal problems, especially brain injury. Vestergaard et al[7,14] suggested that genetics also played an important role in the pathogenesis of febrile seizures in the Danish national cohort. However, because no genealogical information was provided by the Korean NHIS-NSC dataset, we were unable to evaluate the association between genetic factors and febrile seizures. The protective effect of a high income level in the per-person analysis was an interesting finding. The study of Verity et al[15] showed no significant difference in the prevalence of febrile seizures with the educational level or socioeconomic status of the parents in the British national cohort; however, Dalbem et al[6] reported a lower incidence of febrile seizures in higher socioeconomic regions in Brazil. Dalbem et al[6] assumed that the higher socioeconomic regions had better sanitation facilities and thus would have less febrile illness and a lower incidence of febrile seizures. We consider that the lack of proper sanitation and the possibility of higher parental anxiety and family dysfunction could be the reasons for the higher incidence of febrile seizures in the low-income families in this study[16].

In the per-case analysis, a younger age, male sex, presumed pathogen (bacterial), primary infection site (gastrointestinal, genitourinary and unspecified sepsis), cumulative number of

previous febrile seizure episodes and brain injury at birth were associated with an increased risk of febrile seizure. These findings suggest that the risk of febrile seizure is dependent on the characteristics of febrile illness as well as demographics and a previous history of febrile or epileptic seizures. Some former studies have reported a common diagnosis of fever; with the exception of cases with an undetermined focus of fever, a respiratory tract infection was the most common cause of infection, which was consistent with our study result[17,18]. However, the new finding that bacterial infections and sepsis are more common in children with febrile seizures suggests that serious febrile illness may be a risk factor for febrile seizures. Additionally, we classified the infection site and found that patients with gastrointestinal and genitourinary infections were more susceptible to febrile seizures; these findings may have occurred because currently genitourinary infections are considered a common cause of serious bacterial infections in children[19], and gastrointestinal infections caused by rotavirus or norovirus are well-known causes of both febrile and seizures[20,21].

The overall prevalence of epileptic seizure was significantly higher (8.10% vs. 1.28%) if any febrile seizure occurred during the first five years. In addition, the presence of febrile seizure during a febrile illness was associated with an increased risk of a new diagnosis of epileptic seizure (3.29% vs. 0.32%) in children without a previous history of epileptic seizure. Having multiple episodes of febrile seizure (3 cumulative episodes) was an independent risk factor for a new diagnosis of epileptic seizure

within one year after a febrile seizure episode. These findings suggest that the febrile seizure, especially when recurrent, is a significant risk factor for the development of a new epileptic seizure. This result supported the findings of the previous report by Vestergaard et al[7], in which the cumulative incidence of epilepsy after febrile seizure was determined after a 23-year follow-up. Currently, the reason for this association is not clear. One possible explanation may be that the occurrence of febrile seizure at least partially indicates susceptibility to epileptic seizure.

This study has some limitations. First, we could not exclude or distinguish complex febrile seizure such as one with focal onset, one that lasts more than 10 to 15 minutes or recurrent during one febrile illness from the study cases and thus the possibility of misclassification of diagnosis in this population-based study using claim records. These claim records do not provide details of a patient's presentation, and thus a possibility of misdiagnosis exists by proceeding on the assumption that the doctors have correctly entered the diagnosis into the database. Second, because the data source does not include genealogical information, this study is limited to accessing the familial risk factor for the disease. Third, epileptic seizure is not a formal diagnosis of epilepsy requiring long-term antiepileptic medication. Lastly, a small number of febrile seizure cases may be due to Dravet syndrome, which is a rare condition in which seizure areas are frequently triggered by fever[22]. However, this syndrome should have little impact on the results of this study,

because it is a rare condition with a prevalence rate of 1 out of 40,000 worldwide; thus, one or two patients may be present in the study population.

Despite these limitations, this study has several strengths. First, this study was a cohort study in which the enrollees were observed from birth to five years of age. Second, we searched for risk factors of febrile illness from both per-person and per-febrile illness case characteristics to obtain a more comprehensive assessment. Third, the cumulative effect of recurrent febrile seizures is a significant finding for the future diagnosis of epileptic seizures.

Conclusions

In conclusion, the susceptibility to febrile seizure increases with perinatal problems or presumed bacterial infections. In addition, febrile seizures, especially recurrent seizures, are associated with an increased risk of new epileptic seizures. These findings suggest that a febrile seizure is not a completely benign process. More careful patient examination and parental education about the increased risk of epileptic seizure are warranted for children presenting with febrile seizures.

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Appendix

Table A.1. Definition of terms in tables

Terms	Definition
Age of onset	The cohort dataset provides only the year of birth(birth year). The age 0 indicate that the first event occurred at the same year of the birth and age 1 for the next year and so on.
Febrile seizure	A seizure which occurs in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of seizures. We defined ICD-10 code R56.0x as febrile seizure in this study.
Epileptic seizure	A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. We defined ICD-10 code G40.x and G41.x as epileptic seizure in this study.
Brain injury at birth	Outcomes of perinatal injuries of the CNS manifest as the result of the difficult delivery such as skull fracture, hemorrhage or hypoxic-ischemic event. We defined P10.x, P11.x(except P11.5 for Birth injury to spine and spinal cord), P52.x, P91.x or G80.x for the birth-related brain injury.
Presumed pathogen	Suspicious cause of pathogen of febrile illness such as bacterial, viral or others.
Site/type of infection	Suspicious cause of site of infection of febrile illness such as respiratory, gastrointestinal, genitourinary, sepsis, etc.
Category of household income level.	The NHIS-NSC cohort provides household income level of its enrollees in deciles. We categorized it into three including low income level (income level quantile ≤30% or recipients of medical aid program, which is a public assistance program for low-income households) middle-income level(income level quantile

	>30% & ≤70) and high-income level(income level quantile >70%).
New epileptic seizure in a month	ICD-10 code G40.x or G41.x within one month after the visit for febrile illness or febrile seizure which was not entered in the past for the dataset of the patients.
New epileptic seizure in a year	ICD-10 code G40.x or G41.x within one year after the visit for febrile illness or febrile seizure which was not entered in the past for the dataset of the patients.

요 약

2002-2013 한국 건강보험공단 표본 코호트 자료의 종단 분석에 근거한 소아 열성 경련의 위험 인자 및 향후 뇌전증 발작 위험성

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서론 : 열성 경련은 3개월에서 5세 사이의 약 2 - 5 %의 어린이에게 발생하는 비교적 흔한 질병이다. 우리는 한국 소아의 열성 경련의 발병 위험과 발작적인 뇌전증 발작의 위험 인자를 분석하기 위해 인구 기반의 대규모 연구를 수행하였다.

방법 : 2002년부터 2013년 사이의 한국 건강보험공단 표본 코호트 자료를 기반으로 2002년부터 2007년에 태어난 소아의 자료를 수집하였고 이들 중 생후 첫 5년간 생존하지 못한 경우는 연구 분석에서 제외하였다. 열성 경련의 위험 인자는 각 사람 별 (per-person) 및 발열 사례 별 (per-febrile illness case) 로 나누어 분석되었으며, 열성 경련 이후에 발생하는 뇌전증 발작의 위험 증가에 기여하는 요인을 확인하였다.

결과 : 총 54,233명의 소아가 분석에 포함되었고 이들의 열성 경련

의 5년 유병률은 11.19 % 였다. 사람 별 분석에서 남성의 성별, 조산력 및 출생 시의 뇌 손상은 열성 경련의 위험도가 1.17, 1.40, 1.97 (모든 p <0.001) 로 증가했다. 가계 소득이 높은 가정에서 태어난 경우는 열성 경련의 감소하는 경향과 관련이 있었다. 발열 사례 분석에서는 남성의 성별, 출생 시의 뇌 손상, 세균 감염 추정, 위장관의 감염, 비뇨생식기의 감염 및 불특정 패혈증은 열성 경련의 독립적인 위험 인자로 확인되었다. 한 소아에서 열성 경련의 누적 횟수가 많아 질수록, 특히 3회 이상 발생은 마지막 열성 경련 이후 1년 이내로 새로운 뇌전증 발작이 진단될 위험성이 높아짐과 관련이 있었다.

결론 : 성별, 조산력, 출생 시의 뇌 손상, 세균 감염 추정, 위장관의 감염, 비뇨생식기의 감염 및 불특정 패혈증이 한국 소아에서의 열성 경련의 위험 인자로 확인되었다. 이 연구에서 열성 경련의 누적 횟수가 많아질수록 뇌전증 발작이 진단되는 비율이 높아졌다.

주요어 : 열성 경련, 뇌전증 발작, 위험인자
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