Risk of subsequent attention deficit-hyperactivity disorder in children with febrile seizures

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ABSTRACT

Objective In this study, we obtained relevant data from a nationwide cohort database to investigate the risk of attention deficit-hyperactivity disorder (ADHD) in children with a history of febrile seizures (FS).

Methods We identified 1081 children with FS as the case cohort, and the date of diagnosis was used as an index date. Four controls were matched randomly with each case based on age, sex, urbanisation level, parents' occupation, and index date. We applied Cox's proportional hazards regression to estimate the HR and CI of FS-associated ADHD.

Results After 11 years of follow-up, the incidence of ADHD for the FS and control cohorts is 7.83 and 4.72 per 1000 person-years, respectively. The FS cohort was 1.66 times more at risk of ADHD occurrence (95% CI 1.27 to 2.18) than the control cohort. The risk of developing ADHD increased in conjunction with the frequency of FS-related visits.

Conclusions FS may increase the risk of subsequent ADHD occurrence in children. Children who visited physicians for FS more than twice had a significantly higher cumulative incidence of ADHD.

INTRODUCTION

Febrile seizures (FS) have been defined as seizures which occur in children aged between 6 months and 5 years that are accompanied by a temperature of 38°C or higher. Symptoms such as an infection of the central nervous system (CNS), metabolic imbalance, or a history of afebrile seizures episodes have been excluded as FS indicators.¹ FS are the most common seizures that occur in children. Two to five per cent of neurologically healthy infants and children experience at least one FS.

Some parents might consider FS to be detrimental to mental development; however, several investigations, including national population-based studies, have shown that the attention, behaviour, neurocognitive function or scholastic performance of preschool, school-age children and adolescents with a history of FS are similar to those of age-matched controls.^{2–6} Furthermore, Chang *et al*⁷ reported that school-age children with a history of FS had a superior working memory function and control over distractibility and attention. Consequently, FS has been regarded as a benign disorder with good prognosis, although negative effects of FS on mental development have also been reported. For example, preschool children with recurrent FS might have higher risk for delayed expressive language development.⁶

Attention deficit-hyperactivity disorder (ADHD) is a common behavioural neurodevelopmental

What is already known

- ▶ The relationship between febrile seizures (FS) and attention deficit-hyperactivity disorder (ADHD) remains unknown.
- ▶ In this study, we obtained relevant data from a nationwide cohort database to investigate the risk of ADHD in children with a history of FS.

What this study adds

- ▶ Febrile seizures (FS) may increase the risk of subsequent attention deficit-hyperactivity disorder (ADHD) occurrence in children.
- ▶ Children who visited physicians for FS more than twice had a significantly higher cumulative incidence of ADHD.

disorder, especially among boys. Previous community-based research showed that the prevalence of ADHD ranged between 1.7% and 16%, depending on the population and the diagnostic methods.⁸ In Taiwan, a school-based panel study among seventh grade students showed that the prevalence rate of ADHD was 7.5%.⁹ ADHD is characterised by age-inappropriate inattention, hyperactivity and impulsive behaviour. The definitions of ADHD vary in different countries. In Taiwan, ADHD is diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Children of ADHD was defined as children compared with others of the same age and developmental level, beginning developmentally inappropriate behaviour before the age of 7 years, lasting for at least 6 months in two or more settings. In this study, we did not limit the age of diagnosis, because the definition is according to the age of symptoms onset. Children with ADHD typically experience interpersonal relationship problems with family members and peers, as well as poor academic performance and low self-esteem. ADHD is typically associated with other emotional, behavioural, language and learning disorders.

The relationship between FS and ADHD remains unknown. In this study, we examine whether FS is associated with subsequent risk of ADHD in a nationwide population-based cohort.

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METHOD

Data source

We obtained the Longitudinal Health Insurance Database 2000 (LHID2000) from the National Health Research Institutes (NHRI). The NHRI collected and maintained the medical records of the National Health Insurance (NHI) programme for research purposes. NHI was established on 1 March 1995 and provides health insurance for >99% of Taiwan's population. Cheng *et al* had evaluated the accuracy of the National Health Insurance Research Database (NHIRD) in recording ischaemic stroke diagnoses and the NHIRD appears to be a valid resource for population research.^{10 11} The LHID2000 contains 1 million randomly selected insurants from the NHI programme in 2000 and includes all medical records from 1996 to 2010. Although the identification of insurants was recorded before releasing these data to researchers, this study was approved by the China Medical University ethical review committee (CMU-REC-101-012).

Study participants

The section criteria for inclusion in this study are as follows: (1) children aged 6 months to 5 years and (2) newly diagnosed FS (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM): 780.3) between 2000 and 2010. Children with ADHD and hyperkinetic syndrome (ICD-9-CM 314), epilepsy and seizure (ICD-9-CM: 345), myoclonus (ICD-9-CM: 333.2) or convulsions in newborns (ICD-9-CM: 779.0) were excluded. We obtained records for 1081 children with FS as a case cohort and used the date of diagnosed FS as the index date. Four controls were randomly selected from children without FS history before the index date, and they were excluded with the same criteria of the case cohort. We used frequency (group)-matching process to select controls. Controls were with the same frequency of age, gender, urbanisation level, parents' occupation and index date as cases. Because we used frequency-matching process, we performed to use the standard Cox hazard regression for assessing the risk.

The urbanisation level was based on the NHRI¹²; they grouped Taiwan townships into 7 levels (Level 1 was the highest urbanisation, and Level 7 was the lowest). Because few people were categorised as Levels 4 to 7, we grouped them into Level 4. Parents' occupation was grouped into three groups: white collar, blue collar and other.¹³

Statistical analysis

All statistical analyses were conducted using SAS software, V9.2 (SAS Institute Inc, Carey, North Carolina, USA). All tests were two-tailed ($\alpha=0.05$). The χ^2 test and t test were used to test the differences in categorical, included sex, urbanisation level (Levels 1–4) and parents' occupation (white collar, blue collar and other), and continuous variables contained age between two cohorts, respectively. The incidence for ADHD per 1000 person-years was calculated in two groups. Person-years were counted from the index date to the ADHD occurred or the end of 2010. We applied Cox's proportional hazards regression to estimate the HR and 95% CI for FS-associated ADHD and assessed the association between FS frequency visits and ADHD occurrences. The frequency of FS was categorised into three groups (1–2, 3–4 and >4) based on the highest 50%, 50% to 75%, and >75% of frequencies. We applied Kaplan–Meier analysis to plot the cumulative incidence of ADHD, and the log-rank test was used to test the difference between groups. We also tested the Cox proportional hazard assumption using a test of scaled Schoenfeld residuals and the results showed that there was no significant

relationship between Schoenfeld residuals for FS and follow-up time in the model assessing the ADHD risk ($p=0.25$).

RESULT

The record for 5405 people was analysed in this study (FS cohort cases=1081, control cohort=4324). The mean age of children with FS is 2.43 (SD=1.16). In the FS group, there were more boys (58.1%) than girls, more lived in urban areas (54.9%) and more parents were employed in white collar positions (58.8%). There were no significant differences in age, sex, parents' occupation or urbanisation of living areas between the two groups (table 1).

After 11 years of follow-up, the incidences of ADHD for the FS and control cohorts were 7.83 and 4.72 per 1000 person-years, respectively (table 2). The cumulative incidence in case group was approximately 2.5% higher (log-rank $p<0.0001$, figure 1A). The risk of ADHD was 1.66 times greater than that of the control cohort (95% CI 1.27 to 2.18; table 2).

The incidence of ADHD in boys was 3.12 times greater than for girls (7.53 and 2.41 per 1000 person-years, respectively; table 2). Sex-specific HRs were significantly higher, ranging from 1.56 to 2.13 per 1000 person-years in the FS cohort. In stratified analyses by urbanisation level and parents' occupation, the risk was significantly higher compared to the control group, except for those residing in rural areas and other classification of parents' occupation.

Table 3 shows the association between frequency of FS incidence and the development of ADHD. The average frequency of FS-related visits was measured per 5 years. Overall, the risk of ADHD increased from 1.01 to 7.66 (trend test, $p<0.0001$). The risk trend for both genders is identical. Compared to the control cohort, the cumulative incidence for ADHD in children with >4 times and 3–4 FS-related visits increase by approximately 25% and 10%, respectively ($p<0.0001$, figure 1B).

DISCUSSION

A slight predominance of boys was observed in the FS group. Previous studies have reported the proportion of boys as 53%

Table 1 Demographics between children with and without FS

	Febrile seizures				p Value
	No (n=4324)		Yes (n=1081)		
	n	Per cent	n	Per cent	
Age, years, mean (SD)	2.45	(1.17)	2.43	(1.16)	0.67*
Sex					1.00
Boy	2512	58.1	628	58.1	
Girl	1812	41.9	453	41.9	
Urbanisation					1.00
1 (highest)	1096	25.4	274	25.4	
2	1276	29.5	319	29.5	
3	864	20.0	216	20.0	
4	656	15.2	164	15.2	
5 (lowest)	432	10.0	108	10.0	
Occupation					1.00
White collar	2544	58.8	636	58.8	
Blue collar	1200	27.8	300	27.8	
Other	580	13.4	145	13.4	

χ^2 test.

*t test.

FS, febrile seizures.

Table 2 Risk of ADHD compared to children without FS stratified by demographics in Cox's proportional hazard regression

	Non-febrile seizures			Febrile seizures			HR (95% CI)
	ADHD case	Person-years	IR	ADHD case	Person-years	IR	
All	180	38 126	4.72	75	9572	7.83	1.66 (1.27 to 2.18)***
Sex							
Boy	148	21 865	6.77	58	5503	10.54	1.56 (1.15 to 2.12)**
Girl	32	16 260	1.97	17	4070	4.18	2.13 (1.18 to 3.84)*
Urbanisation							
1 (highest)	55	9553	5.76	26	2413	10.77	1.87 (1.17 to 2.98)**
2	56	11 331	4.94	27	2799	9.65	1.96 (1.24 to 3.11)**
3	41	7525	5.45	12	1922	6.24	1.15 (0.60 to 2.18)
4 (lowest)	28	9716	2.88	10	2438	4.10	1.43 (0.70 to 2.94)
Occupation							
White collar	130	22 159	5.87	51	5594	9.12	1.56 (1.13 to 2.15)**
Blue collar	36	10 769	3.34	18	2677	6.72	2.01 (1.14 to 3.54)*
Other	14	5198	2.69	6	1301	4.61	1.73 (0.66 to 4.50)

*p<0.05, **p<0.01, ***p<0.001.

ADHD, attention deficit-hyperactivity disorder; FS, febrile seizures; IR, incidence rate, per 1000 person-years.

and 58.7%,^{6 14} which is consistent with the FS group in this study (58.1%).

FS are typically classified as simple or complex types. ICD-9-CM 780 (febrile convulsion) covered ICD-9-CM 780.31 (simple or unspecified febrile convulsion) and ICD-9-CM 780.32 (complex febrile convulsion). Complex FS is more prolonged (>15 min), focal seizures and/or recurs within 24 h. Because general physicians may be less experienced than paediatricians, they may be unable to differentiate between complex and simple FS cases, which might produce inaccurate results. Previous research showed that children with simple FS and those with complex FS had similar results.³ Therefore, we did not analyse them separately in this study. Based on the definition of FS, neurological or developmental abnormalities before the first FS were included; thus, we excluded only those with a history of epilepsy or afebrile seizures.

Hospital-based studies that selected hospitalised patients or those in specialised clinics with more severe cases identified a higher rate of mental retardation in the FS group.¹⁵ Conversely, the majority of population-based studies showed no difference in prognosis between FS and control groups. These population-based studies using information from questionnaires completed by mothers, children or teachers, intelligence test, behavioural rating and hospital records had covered almost all affected children in general population. However, there may have been some incorrect diagnoses of FS.³ In Taiwan, the diagnosis of ADHD follows DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnostic criteria. Our study was population based, and the data comprised complete records of medical visits. We found that the diagnoses gathered by ICD coding in each medical visit and the frequency of medical visits were more reliable in our study.

Figure 1 Kaplan-Meier analysis estimated cumulative incidence of attention deficit-hyperactivity disorder (ADHD). (A) In children with and without febrile seizures (FS). (B) In different frequency of FS.

Table 3 Risk of ADHD among frequency for FS-related medical visits in Cox's proportional hazard regression

Frequency for medical visit (per 5 years)	ADHD case	Person-years	IR	HR (95% CI)
All				
None	180	38 126	4.72	1.00
1–2	37	7777	4.76	1.01 (0.71 to 1.44)
3–4	16	1179	13.57	2.89 (1.73 to 4.82)***
>4	22	616	35.69	7.66 (4.92 to 11.9)***
p Value for trend				<0.0001
Boy				
None	148	21 865	6.77	1.00
1–2	28	4519	6.20	0.92 (0.61 to 1.38)
3–4	13	579	22.47	3.34 (1.89 to 5.88)***
>4	17	404	41.98	6.29 (3.81 to 10.4)***
p Value for trend				<0.0001
Girl				
None	32	16 260	1.97	1.00
1–2	9	3258	2.76	1.40 (0.67 to 2.94)
3–4	3	600	5.00	2.58 (0.79 to 8.43)
>4	5	211	23.65	12.4 (4.82 to 31.8)***
p Value for trend				<0.0001

***p<0.001.

ADHD, attention deficit-hyperactivity disorder; FS, febrile seizures; IR, incidence rate, per 1000 person-years.

In a prospective population-based case-control study that included 103 children as the sample group, Chang *et al*⁴ reported better control of distractibility and attention at school-age children diagnosed with FS. In a study that used a questionnaire survey of mothers, children with FS were rated as more impulsive or excitable than the control groups, although no significant differences related to inattentiveness or hyperactivity were reported. Verity *et al* considered these results a chance event.³ Regarding the strong genetic factor related to ADHD, Pineda *et al* minimised the genetic factor and found that FS was a risk factor for developing ADHD (OR=2.0) in a genetically isolated community.¹⁶ Our research shows that the risk of ADHD is higher in children with FS (HR=1.66).

The pathophysiology of FS remains unclear. There may be an age-specific increased susceptibility to seizures induced by fever. Genetic and environmental factors play a role in the development of FS. Several FS development mechanisms had been proposed based on animal models or human experiments, including hyperthermia, genetic factors (FEB1-7, FEB9-11), endogenous fever mediators and proinflammatory cytokines.^{17–18}

ADHD is a heterogeneous disorder. In addition to the strong genetic component supported by family, twin and adoption studies, structural/functional abnormality, environmental and immunological factors also interact in these complex brain developmental processes. No single factor is attributable to the expression of ADHD. Dysfunction of the frontostriatal network and dysregulation of the frontal monoaminergic systems and hypothalamic-pituitary-adrenal axis, as well as exposure to lead and zinc may be risk factors.¹⁹

Verity *et al* identified similar intellectual outcomes between children with three or more recurrent episodes and those with fewer than 3.³ However, in our study, children with three or more FS-related medical visits had a significantly increased cumulative incidence of ADHD. The known risk factors of recurrent FS are family history, age of onset (<1 years) and a low degree of fever.¹⁰ There may be a genetic predisposition to FS and ADHD.

There is no known gene involving FS and ADHD. Several studies have indicated that iron deficiency may be related to the

pathophysiology of ADHD.^{21–24} Iron deficiency was considered a risk factor for FS development in several case-control studies, although the pathogenesis remains unclear.^{25–30} Iron deficiency might be the mechanistic link between FS and ADHD.³¹

In our study, a high urbanisation level shows significant ADHD risk for the FS cohort. High urbanisation levels contribute to a modern lifestyle and are also associated with the occurrence of allergies, which are the result of complex gene-environment interactions and proinflammatory cytokines are crucial in an intercellular communication network. Allergic disorders may increase the risk of ADHD in paediatric patients identified by a nationwide population-based study.³² Elevated levels of proinflammatory cytokines, including IL-1, IL-6 and TNF- α at an early age is a risk factor for ADHD.³³ During pre-natal brain development, IL-1 β is a crucial differentiation factor promoting the conversion of mesencephalic progenitor cells into dopaminergic neurones.^{34–35} A recent meta-analysis identified a significant association between IL-1 β -511 C/T gene polymorphism and FS.³⁶ IL- β may be the mechanistic link between FS and ADHD.

Limitation

The strengths of our study include the use of highly representative population-based data. However, specific limitations to our findings should be considered. First, the LHID does not contain detailed information regarding smoking habits, alcohol consumption, socioeconomic status and family history of systemic diseases, all of which may be risk factors for FS or ADHD. Second, the evidence derived from a retrospective cohort study is generally lower in statistical quality than that from randomised trials because of potential bias 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. Third, all data in the LHID are anonymous. Thus, relevant clinical variables, such as blood pressure, imaging results, pathology findings and serum laboratory data, were unavailable. However, data regarding the diagnoses of FS or ADHD were reliable.

CONCLUSION

FS increases the risk of subsequent ADHD in high urbanisation level. Recurrent FS increased the cumulative incidence of ADHD. There may be a common genetic factor between FS and ADHD. Further studies on any correlations among FS, ADHD, iron deficiency or allergic disorders are warranted. Additional research focusing on iron homeostasis or proinflammatory cytokines may identify potential mechanisms.

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