



Febrile convulsions increase risk of Tourette syndrome



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ABSTRACT

Purpose: Febrile convulsion (FC) and Tourette syndrome (TS) are both common neurological disorders in infants and children. Both disorders share clinical similarities, such as paroxysmal symptoms with normal neurodevelopment and expected remission over time. This population-based study investigated the association between FC with TS during childhood neurodevelopment.

Method: We used the Taiwan National Health Insurance Research Database to conduct a retrospective cohort analysis on 1586 FC patients. A reference cohort of 6344 non-FC patients, matched for age, sex, urbanization level, parental occupation, and index year, was used for comparison. The risk of the occurrence of TS in FC patients was assessed using a Cox proportional hazard regression model.

Results: The overall incidence of TS was higher in the FC cohort than in the non-FC cohort (28.5 vs 13.9 per 10,000 person-years; adjusted hazard ratio = 1.91, 95% confidence interval = 1.32–2.75). The associated risk factors for FC patients to develop TS were boys, children living in rural areas, and children whose parents held blue-collar positions. Moreover, the risk of TS in FC patients rose from 0.89 to 16.0 (trend test $P < 0.0001$) when the frequency of FC-related medical visits increased from 1 to 2 times to more than 4 times. The adjusted hazard ratio for TS in related to FC-related medical visits was 1.02 (95% CI = 1.02–1.03) per one frequency increment.

Conclusion: FC may increase the risk of subsequent TS occurrence in children. Children who had frequent medical visits for FC were particularly vulnerable.

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1. Introduction

Febrile convulsion (FC) is the most common seizures in infants and children between the ages of 6 months and 6 years. Accumulated incidence of FC is 2–5% of children by the age of 5 years, with a slight predominance in boys.^{1,2} Several large long-term prospective studies have shown that the majority of patients with FC have a benign outcome with normally developing intelligence and neurodevelopment.^{3,4} Only the subtype of FC that are prolonged or recurrent may be associated with an

increased risk of selected cognitive deficits such as delayed vocabulary development or learning difficulties.^{4–7} However, none of these studies have mentioned an association between FC and Tourette syndrome (TS).

Tourette syndrome, a common neuropsychiatric disorder in children, is characterized by multiple brief, stereotypical, and nonrhythmic movements and sounds.⁸ These clinical symptoms of TS last at least 1 year and often waxes and wanes. The overall prevalence of TS is 0.77% in children, with a strong preponderance in boys.⁹ The mean age of TS onset is approximately 6–7 years, which is older than the onset of FC. Ninety-three percent of TS patients are symptomatic by age 10.⁹ By late adolescence or young adulthood, over one third of TS patients are virtually symptom-free, less than half have minimal to mild symptoms and less than a quarter have persistently moderate to severe symptoms.⁸ Most TS children have normal intelligence but commonly associate with other neuropsychiatric comorbidities, generally comprising

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attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).⁹ Similar to FC, TS children are common in boys, have paroxysmal symptoms and can expect a clinical remission over time. Thus, we suspect these two diseases might have a clinical or consequent association. We used a national population data bank to explore it.

2. Methods

2.1. Data sources

We obtained data from the National Health Insurance Research Database (NHIRD) and the National Health Research Institutes (NHRI) for the Taiwanese National Health Insurance (NHI) program. The NHI program was launched in March 1995, and provides health care to 99% of the 23.74 million residents in Taiwan. The Longitudinal Health Insurance Database contained all of the original claims data of 1,000,000 individuals randomly sampled from the Registry for Beneficiaries of the NHIRD in 2000 (LHID2000), which maintained the registration data of every NHI program beneficiary during the period 1996–2000. There was no significant difference in gender, age or health care costs between cohorts in LHID2000 and all insurance enrollees, as reported by the NHRI in Taiwan. The NHRI followed all of the aforementioned randomly sampled patients to the year 2010. Details of this population-based database have been described elsewhere.¹⁰ The patient identification numbers that were previously used for linking files were scrambled before the dataset was released for research and administrative purposes. Limited data on socio-demographic status, such as sex, birth date, occupation, income level for insurance fee estimates, and area of residence, were also made available. The accuracy and high validity of diagnosis in the NHIRD has been previously demonstrated.^{11,12} This study was exempted by the Institutional Review Board (CMU-REC-101-012). The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) was used to identify health statuses.

2.2. Study design and patients

In this study, we selected infants and children aged 6 months to 6 years, who were diagnosed with FC (ICD-9-CM codes 780.3 excludes 780.33) between 1998 and 2010 as the study cohort. The primary purpose of this study was to determine the association between FC and TS. Hence, we excluded infants and children with a diagnosis of meningitis or encephalitis (ICD-9-CM codes 320–324, 047–049, 062–064), CNS malformation (ICD-9-CM codes 740–742; 330–337), and epilepsy (ICD-9-CM codes 345). The index date for infants and children with FC was the date of their first medical visit. For the comparison cohort, we used a simple random sampling method and selected 4 infants or children without a history of FC before the index date, who were excluded according to the same criteria as those of the study cohort. The FC patients and controls were matched for age (every 1 year), sex, urbanization level, parental occupation, and index year. Apart from common demographic factors, their associated comorbidities were also considered as potential confounding factors between FC and TS. These comorbidities included ADHD (ICD-9-CM codes 314), OCD (ICD-9-CM codes 300.3) and anxiety (ICD-9-CM codes 300.00).

Taiwan launched a national health insurance (NHI) in 1995, operated by a single-buyer, the government. All insurance claims should be scrutinized by medical reimbursement specialists and peer review. According to the revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*, TS may be diagnosed when a person exhibits both multiple motor and one or more vocal tics over the period of a year, with no more than three consecutive tic-free months.¹³ Person-years

of follow-up were calculated for each infant and child until TS (ICD-9-CM codes 307.2) was diagnosed, death occurred, the infant or child withdrew from the insurance system, or until the end of 2010.

2.3. Variables of interest

The socio-demographic variables used in this study comprised age, sex, urbanization level, and parental occupation. White-collar workers were defined as people with occupations characterized by long indoor work hours such as institutional workers, and business and industrial administration personnel. Blue-collar workers were defined as people with occupations characterized by long outdoor work hours, such as fishermen, farmers and industrial laborers. Other occupations included primarily retired, unemployed, or low income populations. The level of urbanization was divided into 4 levels based on the NHRI report (Level 1 was the highest level of urbanization and Level 7 was the lowest. Because few people lived in Levels 5–7, we grouped the least urbanized populations into Level 5). Another variable was the frequency of FC-related medical visits, which were counted when patients visited outpatient/inpatient or emergency department, and had FC in one of the discharge diagnosis. The average frequency was counted per 5 years in the study period.

2.4. Statistical analysis

All analyses were performed using the statistical package SAS for Windows (Version 9.2, SAS Institute Inc., Cary, NC). The Kaplan–Meier method and the log-rank test were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P* value <0.05 was considered statistically significant. Distributions of categorical and socio-demographic factors, including sex, urbanization level, and occupation, were compared between the FC and the non-FC cohorts. The differences were determined using the chi-square test or Fisher-exact test. The mean ages were measured and examined using a Student's *t*-test. The follow-up time (in person-years) was used to estimate incidence rates according to demographic status, urbanization level, and occupation. A Cox proportional hazard regression was used to compare the risk of developing FC-associated TS, in the FC cohort and non-FC cohort. The hazard ratio (HR) and 95% confidence interval (CI) were estimated using the Cox model. Adjusted hazard ratios were also determined after adjusting for potential confounders. This model was also used to assess the association between TS and the frequency of FC-related medical visits. The Kaplan–Meier method was used to plot the cumulative incidence of TS, and a log-rank test was used to compare the cohorts.

3. Results

In total, 1586 FC patients from the NHIRD met our criteria as the FC cohort and 6344 non-FC patients matched based on age, sex, urbanization level and parental occupation were randomly sampled as a non-FC comparison cohort (Table 1). The mean age of the FC and non-FC cohorts were 2.50 ± 1.34 and 2.52 ± 1.36 years, respectively (Table 1). The FC cohort was associated higher incidence of the comorbidities, such as ADHD ($P < 0.0001$), OCD ($P < 0.01$) and anxiety ($P < 0.0001$).

In the FC cohort, TS occurred primarily in boys (9028/15,434, 58.5%), children living in urban areas (8766/15,434, 56.8%), and children with white-collar parents (9219/15,434, 59.7%; Table 2). The overall incidence of TS was higher in the FC cohort than in the non-FC cohort after adjusted for confounders of ADHD, OCD and anxiety (28.5 vs 13.9 per 10,000 person-years; adjusted HR = 1.91,

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