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Trend of subsequent epilepsy in children with recurrent febrile seizures: A retrospective matched cohort study

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ABSTRACT

Purpose: Trends of epilepsy in children were correlated with febrile seizure (FS) in a previous retrospective study. In the present study, the authors obtained relevant data from a nationwide cohort database to investigate trends in subsequent epilepsy in children with a history of recurrent FS.

Methods: A total of 10,210 children with FS comprised the cohort. The diagnosis date was used as the index date. A comparison cohort was randomly matched with each case based on age, sex, urbanization level, parents' occupation, and index date. Cox proportional hazard regression was performed to estimate the hazard ratio and confidence interval of FS-associated epilepsy.

Results: This retrospective cohort study included 7729 children with FS and a comparison cohort of 30,916 children. The incidence of epilepsy was 11.4-fold higher in the FS cohort than in the comparison cohort (5.67 vs. 0.49 per 1000 person-years, respectively). Compared with the comparison cohort, the epilepsy incidence rate ratio increased in children with admissions for FS, from 8.62 at 1 admission to 26.2 at ≥2 admissions (95% CI 6.80–10.9, and 19.78–34.8, respectively; p for trend < 0.0001).

Conclusion: FS may increase the risk for subsequent epilepsy in children. Recurrent FS increased the cumulative incidence of epilepsy.

1. Introduction

Febrile seizure (FS) represents the most common seizure disorder in childhood, and the prognosis is usually benign and self-limiting [1]. The vast majority of children with FS have a normal long-term outcome, and population-based studies show that the absolute risk of unprovoked seizures after febrile seizures is low, which indicates that most FS is an age-specific marker of seizure susceptibility [2,3]. When a simple or complex FS occurs repeatedly, it is considered a recurrent FS and linked to an increased risk of epilepsy [4]. Although the risk factors for recurrence of FS are quite different from the risk factors of subsequent epilepsy, one interesting study found that the risk of epilepsy may be slightly elevated in children with frequent occurrence of simple FS [5].

Determining whether FS can to convert to frank epilepsy has always been in the minds of paediatricians and researchers. The costs to evaluate and treat FS initially depend on the clinical work-up indicated by clinical suspicion. Children with FS do not consume excess health care resources. It was concluded that children with febrile seizures had nearly identical rates of subsequent hospitalisation [11]. Cohort studies

Abbreviations: CNS, central nerve system; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification; NHRI, National Health Research Institute

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showed that the long-term risk of subsequent epilepsy is greater for children with FS, and children with complex FS had a higher likelihood of developing epilepsy [7]. FS in children with pre-existing neurodevelopmental disorders and low parental educational status were known risk factors for subsequent, unprovoked seizure [8]. In addition, an animal study showed that febrile status epilepticus (FS lasting at least 30 min) increased the severity and duration of subsequent, spontaneous seizures compared with simple FS [9].

Early identification of susceptible subgroups could have clinical implications, because these children may need special attention. However, no studies so far have been large enough to evaluate whether the risk of epilepsy after febrile seizures is modified by these factors. The precise knowledge about whether FS are benign phenomena or progress to the development of unprovoked seizures or epilepsy is limited. Surveys on the incidence and risk of epilepsy in children with FS are lacking in Asian populations. Hence, we conducted a retrospective, matched-cohort study for better understanding of the risk of subsequent unprovoked seizures in children with FS in Taiwan.

2. Methods

2.1. Data source

We obtained the children's files from the Taiwan National Health Insurance Research Database (NHIRD). This database was derived from the National Health Insurance (NHI) program, which was set up by the Taiwan National Health Insurance Administration of the Ministry of Health and Welfare and maintained by the Taiwan National Health Research Institutes. Over 99% of the populations in Taiwan are registered in this program. To protect the personal information of the participants, their identifications were recorded in the NHIRD. This study was also approved by the Research Ethics Committee of the China Medical Hospital, Taiwan. The disease was defined according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The children's files, randomly selected from the NHIRD, included all the medical records of the children aged younger than 18 years from 1996 to 2011.

2.2. Study subjects

We collected all the records of 10,210 children who were newly diagnosed with FS (*ICD-9-CM* 780.31) at ages 0.5–5 years, from 2004 to 2008. FS is defined as a seizure occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance or history of an FS [26]. The date of FS diagnosis was defined as the index date. Those with meningitis (*ICD-9-CM* 320–326), encephalitis (*ICD-9-CM* 006.5, 013, 191, 198, 225, 237.5, 239.6 and 294), brain-associated disease (*ICD-9-CM* 310, 331.2, 348, 742, 794, 851 and 959.01) or epilepsy history (*ICD-9-CM* 345) were excluded (n = 2044). The index date for infants and children with FS was the date of their first medical visit. For the comparison cohort, we used a frequency-matched method and randomly selected 4 infants or children without a history of FS before the index date, who were excluded according to the same criteria as those of the study cohort. The FS patients and controls were matched for age (by year), sex, urbanisation level, parental occupation, and index year. For the causal relationship, we excluded patients who developed epilepsy within one year after the index date (n = 437) (Fig. 1). Apart from common demographic factors, their associated neurobehavioural comorbidities were also considered potential confounding factors between FS and epilepsy.

2.3. End point, demographic characteristics and baseline comorbidity

All the children were followed up from the index date until the development of epilepsy. Those who did not develop epilepsy were followed up until the date they turned 18 years old, they withdrew from the NHI program, or the end of 2012, whichever came first. Demographic characteristics included age (0.5–0.9, 1.0–1.9, 2.0–2.9, and 3.0–5.9 years), sex, urbanisation level, and parent's occupation (white collar, blue collar and other). The classified urbanisation level was based on Liu's report, which contained a score calculated by incorporating variables indicating population density (people/km^2) and population ratio of different educational levels, population ratio of elderly, population ratio of agriculture workers and the number of physicians per 100,000 people [10]. Based on Liu's report, the urban areas were grouped into seven levels, with level one the highest urban level and level 7 the lowest urban level. Because only few children lived in the areas at levels 5–7, we combined these children into level 5. Baseline neurobehavioural comorbidities included mental retardation (*ICD-9-CM* 317–319), attention deficit hyperactivity disorder (ADHD; *ICD-9-CM* 314), autism (*ICD-9-CM* 299) and developmental delay (*ICD-9-CM* 315).

2.4. Statistical analyses

The chi-squared test was used to test the difference in demographic characteristics and comorbidities between the FS children and the controls. The *t*-test was used to test the difference in mean age between the two cohorts. The incidence of epilepsy was calculated as follows: the sum of new epilepsy development during the study period divided by the sum of the study subjects exposed to risk during the study period in each cohort. The hazard ratio (HR) and confidence interval (CI) for epilepsy in the FS children in comparison with those in the controls were assessed by using the Cox proportional hazard regression. The multivariable Cox model was adjusted for continuous age, sex, urbanisation levels, parent's occupation and neurobehavioral comorbidities (including mental retardation, ADHD, autism and developmental delay). For sensitivity analyses, the age- (0.5–0.9, 1.0–1.9, 2.0–2.9, 3.0+ years), sex- (boy or girl), urbanisation level- (level 1, 2, 3, 4 and 5), parent's occupation- (white collar, blue collar and other) and comorbidity stratum- (with and without comorbidity) specific epilepsy HR was also calculated by the Cox model. Because the test of the Cox model's assumption, based on examining the relationship between Schoenfeld residuals for epilepsy risk and follow-up time, was violated, the follow-up, duration-stratified analysis was also assessed. The association between epilepsy and FS severity was estimated in all the study subjects, boys and girls. FS severity was grouped into 2 levels, according to the frequency of hospitalisation due to FS. A multivariable Cox proportional hazard regression was used in the trend test between epilepsy and FS severity. The trend test was based on a three-category covariate for FS severity as a continuous independent variable in the Cox regression model and used the significance of the regression coefficient as a linear trend test. The Kaplan-Meier analysis was used to plot the cumulative epilepsy incidence, and the log-rank test was used to test differences between the two cohorts and differences in FS severity. The statistical significance level was set at $p < 0.05$ under a two-tailed test. The SAS version 9.4 statistical software for Windows (SAS Institute Inc., Cary, NC, USA) was used in all the statistical analyses.

3. Results

The data were collected from 2004 to 2008, and the participants were followed from the year of collection until the date of epilepsy development or the end of 2012. The maximum study period was 9 years. In this retrospective cohort study, all 7729 FS cohort children and 30,916 comparison cohort children were included. The mean (standard deviation [SD]) ages of the FS cohort and comparison cohort were 2.25 (1.14) and 2.27 (1.19) years, respectively (Table 1). In the FS cohort, the number of boys was greater than that of girls (59.4% vs. 40.6%), more children lived in higher urban levels (60.3% vs. 39.7%) and more parents had white-collar occupations (60.8% vs. 39.2%).