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Increased risk of epilepsy in children with Tourette syndrome: A population-based case-control study



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ABSTRACT

The association between epilepsy and Tourette syndrome has rarely been investigated. In this retrospective cohort study, we analyzed a dataset of 1,000,000 randomly sampled individuals from the Taiwan National Health Insurance Research Database to determine the risk of epilepsy in children with Tourette syndrome. The study cohort consisted of 1062 patients with Tourette syndrome aged ≤ 18 years, and the control group consisted of three times the number of age- and sex-matched patients without Tourette syndrome, who were insurants, from the same database during the same period. The Tourette syndrome group had an 18.38-fold increased risk of epilepsy than the control group [hazard ratio = 18.38, 95% confidence interval (CI) = 8.26–40.92; $P < 0.001$]. Even after adjusting for the comorbidities, the risk of epilepsy in the Tourette syndrome group with comorbidities remained high (hazard ratio = 16.27, 95% CI = 6.26–18.46; $P < 0.001$), indicating that the increased risk was not associated with comorbidities. This population-based retrospective cohort study provides the first and strong evidence that Tourette syndrome is associated with a higher risk of epilepsy. A close follow-up of children with Tourette syndrome for the development of epilepsy is warranted.

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What this paper adds?

This population-based retrospective cohort study provides the first and strong evidence that Tourette syndrome is associated with a higher risk of epilepsy.

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1. Introduction

Tourette syndrome is characterized by multiple motor tics with at least one vocal tic; moreover, these tics must occur multiple times in a day intermittently or continuously for at least 1 year. They must also have been manifested before the age of 18 years. The overall prevalence of Tourette syndrome is 1%, with an increased prevalence in Western countries. Epidemiological studies report that Tourette syndrome affects 1–3.8% of school-age children in Western countries and only approximately 0.46–0.56% in Asian countries (Taiwan and China) (Robertson, Eapen, & Cavanna, 2009).

Studies have also reported a high rate of psychiatric comorbidities among Tourette syndrome cohorts, including attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD) (Freeman et al., 2000; Robertson et al., 2009). Epidemiological studies have reported the incidence of ADHD among children with Tourette syndrome to be as high as 60–80%. Approximately 11–80% had comorbid OCD, 22.7% had comorbid learning difficulties, 25% had comorbid migraine, and roughly 36–40% had comorbid anxiety disorder (Cavanna et al., 2011; Du et al., 2010; Freeman et al., 2000; Kwak, Vuong, & Jankovic, 2003). This finding leads to the concept that Tourette syndrome is a “spectrum” rather than a unitary condition, a concept that extends Tourette syndrome to include different psychiatric problems (Cavanna & Rickards, 2013). Most of these comorbidities begin early in life (between 4 and 10 years) (Hirschtritt, Lee, & Pauls, 2015) and are the major cause of functional impairment in the affected subject. The comorbidities of Tourette syndrome are associated with an increased risk of epilepsy (Chou et al., 2013; Lhatoo & Sander, 2001; Tuchman & Rapin, 2002). However, only few studies have reported an association between Tourette syndrome and epilepsy (Diamond, Kenney, & Jankovic, 2006; Doherty & Sloan, 2010; Lin, Hsu, Wang, & Shen, 1989; Rizzo, Gulisano, Cali, & Curatolo, 2010). Rizzo et al. (2010) reported a case series of eight patients with Tourette syndrome presenting with the comorbidities ADHD and epilepsy. Most of these patients developed epilepsy before the onset of Tourette syndrome, which was easily controlled by medications. However, a study with a large sample size investigating the risk of epilepsy among children with Tourette syndrome is lacking.

The pathogenic mechanisms of Tourette syndrome remain unclear, although several hypotheses have been proposed, including the dysfunction of basal ganglion-related circuits, and abnormalities of the dopamine system (Du et al., 2010; Leckman & Riddle, 2000). Besides, malfunctioning of the cortico-striato-thalamo-cortical circuits and alteration of the neuromodulatory system, including the dopamine system, have also been linked to seizures (Bozzi & Borrelli, 2013; Chang & Lowenstein, 2003; Ciumas, Wahlin, Espino, & Savic, 2010; Kostopoulos, 2001). However, whether there is a close relationship between Tourette syndrome and epilepsy remains to be investigated. In the present study, we conducted a population-based retrospective cohort study to determine whether there is an increased risk of epilepsy in children with Tourette syndrome.

2. Methods

2.1. Data sources

We used data from the National Health Insurance Research Database (NHIRD), which was released by the Taiwan National Health Research Institutes (NHRI) (Fig. 1). Taiwan launched its single-payer National Health Insurance (NHI) program in March 1995, covering approximately 99% of Taiwan's 23.74 million residents in 2009. We analyzed data from the Longitudinal Health Insurance Database (LHID 2005) of the National Health Research Institutes that included a cohort dataset of 1,000,000 randomly sampled individuals who were still alive in 2005. There were no statistically significant differences in terms of age, sex, and healthcare cost distribution among the patients in the LHID 2005 and the original NHIRD. The NHIRD uses the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) to identify the diagnosis of disease and provides one principal diagnosis and other two/four secondary diagnoses for outpatient/inpatient records. The Institutional Review Board of the National Taiwan University Hospital approved this study.

2.2. Study population

Patients with newly diagnosed Tourette syndrome (ICD-9-CM codes 307.2) from 2001 to 2007 were selected for data analysis, and their index dates were used as dates of diagnosis. In addition, the index date of the control group was set to the middle date of the same month of the index date in the Tourette syndrome group. We ascertained the age by subtracting the birth date from the corresponding index date. Patients with a previous diagnosis of epilepsy (ICD-9-CM code 345.xx) before the index date were excluded from the study. The control group consisted of three times the number of age- and sex-matched children without Tourette syndrome, who were insured, from the same database during the same period; the individuals were selected using the same exclusion criteria. Each patient was followed up for 3 years after the diagnosis of Tourette syndrome for the development of epilepsy. Details regarding the comorbidities, including depression (ICD-9-CM codes 296.2x, 296.3x, 300.4), anxiety disorder (ICD-9-CM code 300.xx), ASD (ICD-9-CM code 299.0x), conduct disorder (ICD-9-CM codes 312.xx, 313.81), bipolar disorder (ICD-9-CM codes 296.0x–296.1x, 296.4x–296.9x), sleep disorder (ICD-9-CM codes 307.4x, 780.5x), OCD (ICD-9-CM codes 300.3), learning difficulties (ICD-9-CM codes 315.0x–315.2x, V40.0), ADHD (ICD-9-CM code 314.xx), and migraine (ICD-9-CM codes 346.0x–346.9x), were collected from the NHIRD.

For the urbanization level, we used the four-level notation according to the standards established by the Taiwanese NHRI (Liu, Hung, & Chuang, 2006). Level 1 was defined as the most urbanized area and level 4 as the least urbanized. The criteria on

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