



Increased risks of tic disorders in children with epilepsy: A nation-wide population-based case–control study in Taiwan



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ARTICLE INFO

Article history:

Received 6 July 2015

Received in revised form 18 October 2015

Accepted 22 October 2015

Available online 12 November 2015

Keywords:

Tourette syndrome

Tic disorders

Epilepsy

Comorbidity

Children

ABSTRACT

Both epilepsy and tic disorders may share common mechanisms with the involvement of abnormal cortical-basal ganglion circuit connection and dopaminergic dysfunction. However, the association between epilepsy and tic disorders has never been studied. This study investigated the risks of developing tic disorders among children with epilepsy using databases of a universal health insurance system in Taiwan.

The data analyzed in this study were retrieved from the National Health Insurance Research Database in Taiwan. The study cohort included children with epilepsy between 2001 and 2007 ($n = 2629$) and a three-fold age- and gender-matched controls ($n = 7887$). All subjects were followed up for 3 years from the date of cohort entry to identify their admissions due to tic disorders (ICD-9-CM codes 307.2, 307.20–307.23). Cox hazard regression analysis was performed to estimate the effect of epilepsy on the occurrence of tics.

The epilepsy cohort had a higher prevalence of tics (1.7% vs. 0.2%), and a 8.70-fold increased risk of developing a tic disorder compared with the controls (adjusted hazard ratio (AHR) 8.70, 95% confidence interval (CI) 4.26–16.37, $p < 0.001$). Male patients were observed to have a higher risk of developing a tic disorder (AHR 1.90, 95% CI = 1.04–3.46, $p < 0.001$) compared to female individuals. Patients with multiple antiepileptic drugs treatment also exhibited higher crude OR for developing tic disorders.

This nationwide population-based cohort study, for the first time, demonstrated that there is a significantly increased risk for tic disorders among children with epilepsy. We also found males, attention deficit disorder and the use of multiple AEDs to be independent risk factors of tic disorders. Closely evaluating possible tic disorders would be crucial for improving the outcome and life quality in children with epilepsy.

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What the paper adds?

- This is the first population-based case–control study showing the association of tic disorders with epilepsy.

1. Introduction

Epilepsy is one of most common neurologic disorders in children, with approximately 5–10 children per 1000 affected (Shinnar & Pellock, 2002). Children with epilepsy often exhibit numerous developmental neuropsychiatric comorbidities, including autistic spectrum disorders and attention-deficit hyperactivity disorder (ADHD) (Lin, Mula, & Hermann, 2012; Russ, Larson, & Halfon, 2012), which can interfere with treatment strategies and reduce their quality of life compared with that of the general population (Eddy et al., 2010). It is crucial to develop a better understanding of the burden of neuropsychiatric comorbidities in childhood epilepsy in order to improve the quality of life of those affected and identify the shared neurobiological mechanisms underlying multiple comorbidities.

A tic is a rapid, involuntary, stereotyped, and non-rhythmic movement or phonic production. Tic disorders, which include chronic tic disorder and Tourette syndrome (TS), are extremely common in children, with epidemiological studies showing that about 20% of school-aged children exhibit isolated and transient tics (Scahill, Specht, & Page, 2014). TS, a common childhood onset neurobehavioral disorder that reportedly affects 2.6–38 children per 1000, is defined by the presence of multiple motor tics and at least one vocal tic at some time for more than a year (Scahill et al., 2014). Children with TS exhibit clinical diversity and often suffer from various neurodevelopmental comorbidities, including ADHD, learning difficulties, obsessive-compulsive disorders (OCDs), autistic spectrum disorders, and coexistent psychopathologies such as anxiety and depression, which appear to negatively impact their quality of life more than the severity of their tics (Cavanna, Servo, Monaco, & Robertson, 2009; Mol Debes, 2013; Rizzo, Gulisano, Cali, & Curatolo, 2012). Although the pathophysiology that gives rise to the clinical heterogeneity and related neurodevelopmental comorbidities remains unclear, converging evidence suggests that abnormal cortical-basal ganglion circuit connections and dopaminergic systems are involved (Jankovic & Kurlan, 2011). Substantial evidence from the study of epilepsy also suggests that altered dopaminergic neurotransmission and the corticostriatal network are involved in the disorder (Avchalumov, Kirschstein, & Kohling, 2011; Bouillere et al., 2008; Bozzi & Borrelli, 2013; Cifelli & Grace, 2012; Ciumas, Wahlin, Espino, & Savic, 2010; Landvogt, Buchholz, Bernedo, Schreckenberger, & Werhahn, 2010; Rektor, Kuba, Brazdil, & Chrastina, 2012; Rocha et al., 2012; Slaght et al., 2004). Therefore, it is reasonable to propose that a correlation exists between epilepsy and tic disorders in children. Furthermore, reports of the effectiveness of antiepileptic drugs (AEDs) such as topiramate in the management of tic disorders indicate that the disorders potentially share similar pathophysiologic mechanisms (Jankovic, Jimenez-Shahed, & Brown, 2010). However, the association between epilepsy and tic disorders remains to be fully investigated. In this study, we investigated the correlation between epilepsy and tic disorders and evaluated their relationships with comorbidities and the use of AEDs.

2. Materials and methods

2.1. Source of data

In this study, we used the National Health Insurance Research Database (NHIRD), which has been collecting nationwide healthcare data since the implementation of the Taiwan National Health Insurance (NHI) program in 1995. By 2009, the NHI program had integrated all public insurance systems and covered all inpatient and ambulatory medical claims for approximately 99% of the Taiwanese population.

The data used in this work was obtained from the Longitudinal Health Insurance Database (LHID 2005), which is a subset of the NHIRD. The LHID2005 consists of all the original medical claims for 1,000,000 enrollees' historical ambulatory and inpatient care data from 1997 to 2010. To keep individual information confidential, all personal identification numbers in the data were encrypted. The NHRI reported that there were no statistically significant differences in age, sex, and healthcare cost distribution between the randomly sampled group and the original NHIRD. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) was used to identify the diagnosis of a given disease.

Because the database we used consists of de-identified secondary data released for research purposes, the Institutional Review Board of National Taiwan University Hospital agreed to allow the present study to be conducted.

2.2. Study design and populations

In this work, a cohort study design was used to examine the relationship between epilepsy and the risk of developing a subsequent tic disorder. Patients were considered to belong to the study cohort if they had been diagnosed as having

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