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Comorbidities and risk factors associated with newly diagnosed epilepsy in the U.S. pediatric population

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ABSTRACT

Neurobehavioral comorbidities can be related to underlying etiology of epilepsy, epilepsy itself, and adverse effects of antiepileptic drugs. We examined the relationship between neurobehavioral comorbidities and putative risk factors for epilepsy in children with newly diagnosed epilepsy. We conducted a retrospective analysis of children aged ≤18 years in 50 states and the District of Columbia, using the Truven Health MarketScan® commercial claims and encounters database from January 1, 2009 to December 31, 2013. The eligible study cohort was continuously enrolled throughout 2013 as well as enrolled for any days during a baseline period of at least the prior 2 years. Newly diagnosed cases of epilepsy were defined by *International Classification of Diseases, Ninth Revision, Clinical Modification*-coded diagnoses of epilepsy or recurrent seizures and evidence of prescribed antiepileptic drugs during 2013, when neither seizure codes nor seizure medication claims were recorded during baseline periods. Twelve neurobehavioral comorbidities and eleven putative risk factors for epilepsy were measured. More than 6 million children were analyzed (male, 51%; mean age, 8.8 years). A total of 7654 children were identified as having newly diagnosed epilepsy (125 per 100,000, 99% CI = 122–129). Neurobehavioral comorbidities were more prevalent in children with epilepsy than children without epilepsy (60%, 99% CI = 58.1–61.0 vs. 23%, CI = 23.1–23.2). Children with epilepsy were far more likely to have multiple comorbidities (36%, 99% CI = 34.3–37.1) than those without epilepsy (8%, 99% CI = 7.45–7.51, $P < 0.001$). Preexisting putative risk factors for epilepsy were detected in 28% (99% CI = 26.9–29.6) of children with epilepsy. After controlling for demographics, neurobehavioral comorbidities, family history of epilepsy, and other risk factors than primary interest, neonatal seizures had the strongest independent association with the development of epilepsy (OR = 29.8, 99% CI = 23.7–37.3, $P < 0.001$). Compared with children with risk factors but no epilepsy, those with both epilepsy and risk factors were more likely to have intellectual disabilities (OR = 13.4, 99% CI = 11.9–15.0, $P < 0.001$). The epilepsy and intellectual disabilities could share the common pathophysiology in the neuronal network.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, having a significant public health burden [1–3]. Children are the largest subpopulation with newly diagnosed epilepsy [4]. Recurrent epileptic seizures compromise health, development, education, and quality of life [5–7]. Furthermore, a variety of neurobehavioral comorbidities may adversely affect life performance and quality of life as much or more than seizures themselves [8–13]. Despite intellectual disabilities and behavioral disorders that are commonly known to coexist in children with newly diagnosed epilepsy [9,14–16], relationships between neurobehavioral comorbidities and risk factors for epilepsy remain to be delineated in children with newly diagnosed epilepsy.

Using a U.S. large nationwide healthcare claims database, we sought to determine if there is a difference in the occurrence of neurobehavioral comorbidities between children with and without risk factors for epilepsy. We also sought to estimate the conditional risk for neurobehavioral comorbidities given the presence of epilepsy and risk factors for epilepsy, while controlling for age, sex, residence, and family history of epilepsy.

2. Methods

2.1. Study population

We conducted a retrospective observational study of children aged 0–18 years enrolled between January 1, 2009 and December 31, 2013

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in the Truven Health MarketScan® commercial claims and encounters database, which collects data from across the United States. The database contains information from active employees, early retirees, the Consolidated Omnibus Budget Reconciliation Act (COBRA) continues, and their dependents insured by employer-sponsored healthcare plans. The information captures person-specific enrollment records with demographics and enrollment status, clinical utilization, and expenditures across inpatient, outpatient, and pharmaceutical dispensing care venues.

All data are compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was approved and Institutional Review Board (IRB) exemption was obtained by the Emory Institutional Review Board.

2.2. Inclusion criteria and case identification

We included children 0–18 years of age in 50 states and the District of Columbia, who were continuously enrolled throughout 2013 as well as enrolled for any days during at least the prior 2 years. Subjects under 1 year of age needed no prior year of enrollment, while those aged 1 to <2 years required at least 1 prior year of enrollment (Fig. 1).

Epilepsy cases were defined consistent with the guidelines of the International League Against Epilepsy (ILAE) Epidemiology Commission [17] and a computer algorithm developed for detecting epilepsy cases [18]. Using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and antiepileptic drug claims, we identified a case of epilepsy if it met any of the following criteria: 1) an occurrence of ≥2 ICD-9-CM codes 345.xx among separate medical encounters on separate dates; 2) an occurrence of ≥1 ICD-9-CM codes 345.xx and ≥1 ICD-9-CM codes 780.39 among separate medical encounters on separate dates; 3) an occurrence of 1 ICD-9-CM code 345.xx and code(s) for antiepileptic drug prescription; and 4) an occurrence of ≥2 ICD-9-CM codes 780.39 among separate medical encounters on separate dates and code(s) for antiepileptic drug prescription [19,20]. Subjects with newly diagnosed epilepsy were defined as those who satisfied the epilepsy case definition in 2013 but with neither seizure codes nor seizure medication claims during their baseline periods.

We identified twelve neurobehavioral comorbidities and eleven putative risk factors for epilepsy from the literature. The neurobehavioral comorbidities included intellectual disabilities (mental retardation, specific delay in development, delayed milestones, and problem with learning), psychiatric & behavioral disorders (hyperkinetic syndrome of childhood, conduct disorder, behavioral problem, anxiety & emotional disturbances, depression, and autism), and headache & migraine. A case of comorbidity was defined as a subject having ≥1 corresponding ICD-9-CM codes of comorbidity in either 2013 or any previous years. The putative risk factors for epilepsy included short gestation & low birth weight, traumatic brain injury, congenital anomaly, metabolic disorder, childhood static encephalopathy (i.e., cerebral palsy), central nervous system (CNS) infection, Malignant tumor or other brain tumors, stroke or cerebrovascular disease, perinatal morbidity, and neonatal seizures. Subjects were determined as having a preexisting risk factor for epilepsy if ≥1 corresponding ICD-9-CM codes of risk factor were recorded either before the epilepsy index date or <90 days after the epilepsy index date. The epilepsy index date was determined by the first appearance of ICD-9-CM code 345.xx or the second appearance of ICD-9-CM code 780.39.

2.3. Other variables of interest

Demographic variables included sex, age, and residence. Age was categorized into the following four groups: 0–4, 5–9, 10–14, and 15–18 years of age. Based on the 2010 U.S. Census [21], subjects' residential areas were divided into three groups, including metropolitan statistical areas (MSAs) with a population of ≥1 million, MSAs with a population of <1 million, and non-MSAs. The Truven Health MarketScan® database

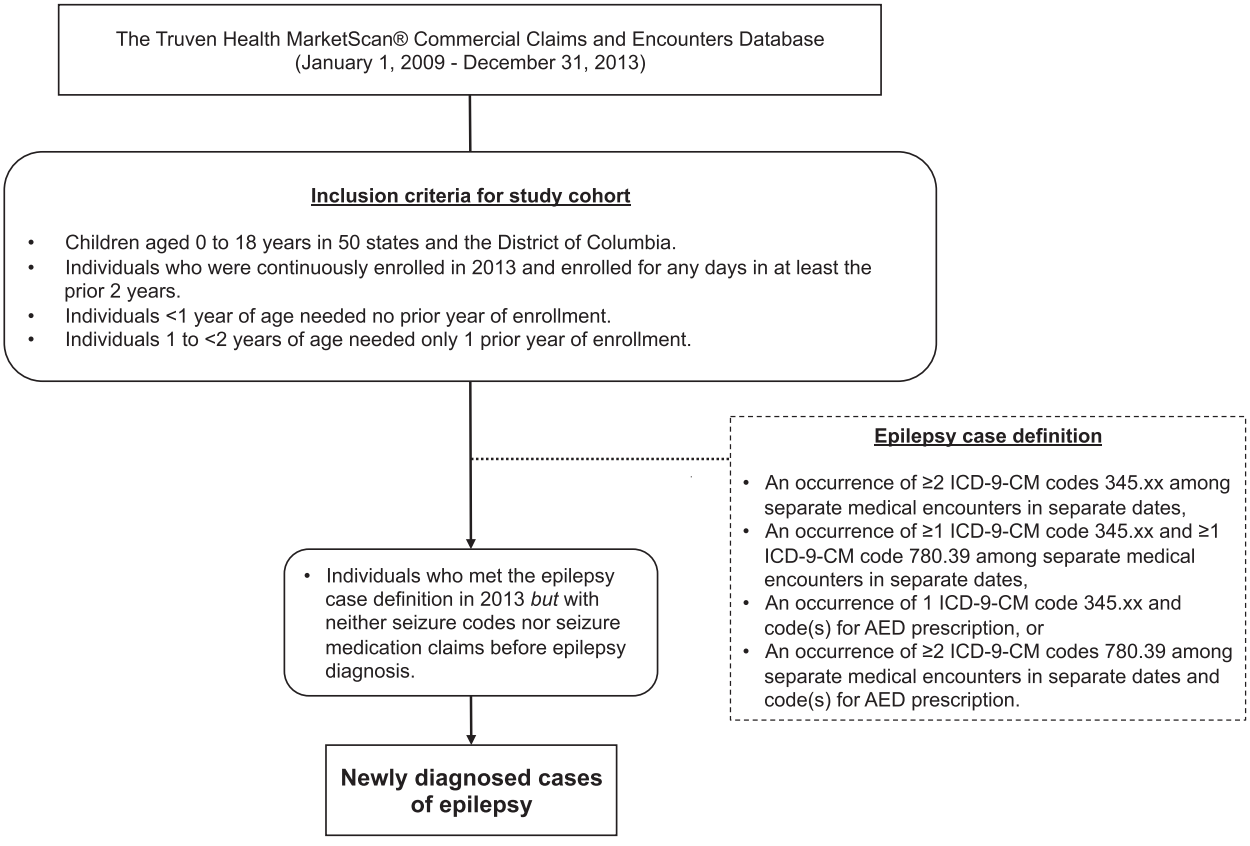

Fig. 1. Study flow diagram.