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Epilepsy in tuberous sclerosis patients in Sweden – Healthcare utilization, treatment, morbidity, and mortality using national register data

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ABSTRACT

Purpose: This study is designed to estimate the prevalence of epilepsy associated with TSC in Sweden and to describe treatment, morbidity, and mortality of TSC patients with epilepsy.
Methods: Register data for 2004–2014 was obtained from the National Board of Health and Welfare in Sweden. Patients with TSC were identified using ICD-10 codes. Epilepsy was identified using ICD-10 codes, interventions aimed to treat epilepsy, or prescriptions for antiepileptic drugs.
Results: The prevalence of TSC was 5.38 per 100 000 individuals. We identified 551 unique patients with TSC, of which 386 (70.1%) had epilepsy. The mean study period was 8.82 years. Antiepileptic drugs were dispensed to 97.9% of patients with epilepsy. The most prescribed antiepileptic drug was sodium valproate. Ketogenic diet was used in 6 (1.6%) patients, vagus nerve stimulation in 23 (6.0%) patients, and epilepsy surgery was performed in 25 (6.5%) patients.
The mean number of outpatient visits per year was 4.70 (SD 4.17) and the mean number of inpatient days per year was 3.25 (SD 5.61). The mean number of outpatient visits per year with an ICD-10 code for epilepsy was 1.65 (SD 1.95) and the corresponding number of inpatient days was 2.06 (SD 4.50). A total of 30 patients with TSC and epilepsy died during the study period.
Conclusions: The prevalence of epilepsy in this study was in the lower range of previously reported numbers, suggesting that epilepsy may be overestimated in non-population based studies. A substantial part of the healthcare utilization was directly related to epilepsy.

1. Introduction

Tuberous sclerosis complex[1] (TSC) is a rare genetic disorder characterized by the presence of benign tumors (hamartomas) in multiple organs, including the brain, kidneys, heart, and skin [1]. In 85–90% of the patients with a clinical diagnosis of TSC, a pathogenic mutation is found in either of the tumor suppressor genes TSC1 or TSC2 [2,3]. In the remaining patients, it has been suggested that the mutation is mosaic or in non-coding regions of these genes, suggesting there are no other TSC genes [4]. TSC can be inherited, but is a de novo event in the majority of patients [5]. Cortical tubers, subependymal nodules (SEN), and subependymal giant cell astrocytomas (SEGA) are neuropathological hallmarks of TSC. The presence of cortical or subcortical tubers is associated with the development of epilepsy, which is the most common neurological manifestation of TSC, with a reported prevalence as high as 90% in some studies [5–7]. Epilepsy is already present at the time of TSC diagnosis in up to two thirds of the patients, as it often debuts during the first year of life with focal seizures or epileptic spasms (spasms occurring in infancy are referred to as infantile spasms; IS) [5]. Multiple seizure types may develop, and seizures are often refractory to treatment [2,5,8,9]. The early onset and refractory nature of epilepsy in TSC is of concern, as there is a correlation between severe/early on-set epilepsy and intellectual

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[1] Shared authorship.
[1] AED Anti-Epileptic Drug, ATC Anatomical Therapeutic Chemical, CDR Cause of Death Register, ES Epileptic Spasms, IS Infantile Spasms, mTOR Mechanistic Target of Rapamycin, mTORC1 Mechanistic Target of Rapamycin Complex-1, NBHW National Board of Health and Welfare, NPR National Patient Register, PDR Prescribed Drug Register, SEGA SubEpendymal Giant cell Astrocytoma, SEN SubEpendymal Nodule, TAND TSC Associated Neuropsychiatric Disorder, TSC Tuberous Sclerosis Complex, VNS Vagus Nerve Stimulation

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disability, underlining epilepsy as a major cause of morbidity in the TSC population [3,5,7]. Treatment options for epilepsy associated with TSC generally mirrors that of epilepsy in the general population. First-line treatment is an anti-epileptic drug (AED) and second-line treatment combines AEDs [10]. The use of ketogenic diet, vagus nerve stimulation (VNS), and epilepsy surgery are treatment options of refractory epilepsy [2,9–12]. The mutation in TSC1 or TSC2 leads to insufficient suppression of the mechanistic target of rapamycin (mTOR) complex-1 (mTORC1) pathway, which results in the growth of hamartomas [3]. Inhibiting the mTORC1 pathway is a viable approach for the treatment of TSC associated epilepsy. Recent evidence supports mTOR-inhibitors as adjunctive treatment to AEDs for treating epilepsy in TSC patients [13]. Given the prevalence and severity of TSC-associated epilepsy there is a need to study patients with the condition in any given setting. The aim of this study is to describe prevalence, manifestations, treatments, healthcare utilization, and mortality of TSC patients with epilepsy in Sweden using population based registers.

2. Material and methods

2.1. Study design

This study used registers held by the National Board of Health and Welfare (NBHW) to study patients with TSC and epilepsy. The selected registers included a national in- and outpatient register (National Patient Register, NPR), the national Prescribed Drug Register (PDR), and the national Cause of Death Register (CDR). The registers contain healthcare visits, all dispenses of prescribed pharmaceuticals, and mortality including causes of death. All selected registers are national with mandatory reporting for healthcare providers and pharmacies. The NBHW reports close to complete coverage with 99% of inpatient discharges being recorded and only 1–2% missing in the CDR [14,15].

The NPR contains data on all healthcare utilization except primary care, including length of stay, International Classification of Diseases (ICD-10) codes, and procedure codes. The PDR contains data on the date of prescription, dispense, and Anatomical Therapeutic Chemical (ATC) codes of all dispensed drugs. Non-prescription pharmaceuticals and pharmaceuticals distributed to patients within healthcare institutions are not included in the PDR. The CDR contains data on underlying and accompanying cause of death along with supporting information such as recent surgical procedures.

Individuals were identified in the NPR. All patients with an ICD-10 code for TSC, Q85.1, from the 1st of January 2004 to the 31st of December 2013 were included. Epilepsy was defined as at least one occurrence of an ICD-10 code for epilepsy, G40.* or G41.*, a procedure directly related to epilepsy (VNS, ketogenic diet, or epilepsy surgery), or retrieval of an AED, ATC-code: N03A*.

For the identified individuals, all pharmaceutical dispenses, healthcare visits (inpatient and outpatient), and deaths were extracted from the PDR, NPR, and CDR. All data in the study period was obtained, regardless of when the first TSC or epilepsy observation was identified.

2.2. Study period

The study period was the 1st of January 2004 to the 31st of December 2014. Due to differences in availability, update frequency, and latency, all registers did not cover the entire period. The actual study period for each register is depicted in Fig. 1. Individuals were identified as having TSC in the NPR, i.e. the identification period corresponds to the study period for the NPR. The PDR did not include the Swedish personal identification number prior to 1st of July 2005, only allowing for coupling with the NPR after that date. The CDR lacks specific data on cause of death for 2014 as this is updated retrospectively and was not available at the time of data extraction.

2.3. Analysis

For the identified population we studied the prevalence of TSC manifestations, pharmaceutical utilization, healthcare utilization, non-pharmaceutical procedures, and mortality. The prevalence of TSC and epilepsy is limited to clinically relevant cases as only patients with at least one corresponding healthcare visit are included. Refractory epilepsy was defined as having more than two simultaneous AEDs for at least 91 days, corresponding to at least two consecutive prescription periods [16]. Prescribed pharmaceuticals were defined using ATC-codes. Specific attention was paid to drugs relating to the nervous system: AEDs (N03A*), neuroleptics (N05A*), anxiolytics (N05B*), and psychoanaleptics (N06*). Use of mTOR inhibitors was also captured. Any retrieval of AEDs (N03A*) was assumed to last for 90 days according to national recommendations [17].

Healthcare utilization was defined as the number of outpatient visits and inpatient days during the study. General healthcare and episodes with a diagnosis of epilepsy were recorded separately. The number of outpatient visits and inpatient days per year is presented as means with standard deviations. Healthcare per year was only calculated for individuals with a study period of at least 90 days in the NPR.

Non-pharmaceutical procedures and interventions were identified using procedure codes (KVÅ/KKÅ). The number of individuals

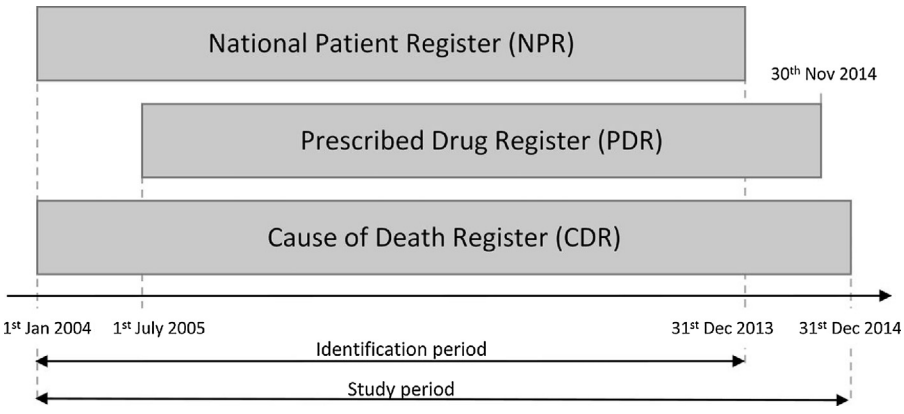

Fig. 1. Study Period.