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Electroconvulsive therapy and subsequent epilepsy in patients with affective disorders: A register-based Danish cohort study

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ABSTRACT

Objective: It has been suggested that Electroconvulsive Therapy (ECT) might increase the risk of epilepsy but the few patient studies with retrospective data from medical records do not support the hypothesis. The aim of this study was to examine the relationship between ECT and subsequent incident epilepsy in patients with affective disorder. We also explored whether any association varied with number of ECTs and time since last treatment.

Methods: All 169,457 patients with first hospital contact for an affective disorder between January 2005 and December 2015 were identified in the Danish National Patient Registry and followed for incident epilepsy from January 2005 until November 2016. The association between ECT and epilepsy was examined using Cox proportional hazard regression with adjustment for gender, age, educational level, comorbid schizophrenia, previous stroke and antidepressant and antipsychotic medication use.

Results: A total of 5875 patients had at least one ECT and 1873 patients developed epilepsy (Incidence rate: 213 pr. 100,000 person years) during the follow-up of mean 5 years. In patients below age 40 years, ECT was associated with a higher rate of epilepsy after adjustment for covariables (Hazard Ratio (HR) = 1.84; 95% Confidence Intervals (CI) = [1.24–2.74]). In patients aged 41–60 years ECT was not associated with epilepsy, while for those above 60 treated with ECT the rate was lower (HR = 0.57; (95% CI = [0.37–0.89]).

Conclusion: In patients with affective disorders, we found a weak positive association between ECT and subsequent diagnosis of epilepsy in those younger than 40 years, and a weak negative association in patients older than 60 years. The associations might be subject to residual confounding from risk factors related to ECT.

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Introduction

Since its introduction in 1938, Electroconvulsive therapy (ECT) has been used worldwide when treating acute and life-threatening neuro-psychiatric illness [1,2]. The beneficial effects of ECT are well documented but there are ongoing discussions regarding potential adverse neurological outcomes [3,4]. The interest of a possible association between ECT and epilepsy was initiated by experimental studies in 1960es providing contradictive findings where some

indicated that repeated ECT might protect against spontaneous fits [5,6], while others suggested that repeated, spaced electrical stimulation might cause epilepsy in rats by a so called kindling effect [7]. In 1980 Blackwood et al. [8] published data from a historical cohort with 166 patients treated with ECT in Scotland in 1971 and 1976. Of them 5 had epilepsy corresponding to a prevalence of 3% (95% confidence intervals 0.4–5.6), which, however, was less than the prevalence of epilepsy in the background population (5.5%). Few years later a review of 19 studies with all reported cases of ECT-induced epilepsy during the period 1938–1980 was published [9]. There was 81 epileptic episodes among presumed 71,052 ECT-treated patients, but the estimated incidence rate for epilepsy for the ECT-treated at 114 per 100,000 did not differ

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Abbreviations

DNPR Danish National Patient Registry

significantly from the incidence rate in a general population. Thus, the authors concluded that the seizures were more related to patient' underlying medical status rather than treatment features. More than two decades later the question of any ECT-epilepsy association was raised again. In an American case study from 2007, Rasmussen & Lunde [10] reviewed the medical records for more than 3000 maintenance-ECT over a decade and found four patients who developed epilepsy. On this basis, the authors were not able to determine whether ECT played any role in the development of the epileptogenic activity. In the most recent study published in 2013, Ray reported results from retrospectively collected data on 619 patients with no family history of seizures, mental retardation or abuse who had received ECT in India between 1990 and 1995, and were followed for 10 years but no cases of epilepsy were registered [11]. In addition, one patient study has indicated that ECT might have anticonvulsant properties [12], but this has not been replicated by others [13], and the mechanisms responsible for any such action remain unknown [14]. Thus, the available evidence for an association between ECT and epilepsy is inconsistent and based on retrospective reviews of medical records, and it is not clear how complete patients have been followed for epilepsy outcomes. Furthermore, in these studies there was no reference group in order to set the data in perspective to patients who did not receive ECT.

Consequently, the aim of this study was to examine the association between ECT and epilepsy in a large cohort of patients with a first-time hospital diagnosis of affective disorders. As seizure threshold is suggested to increase with age [15] and number of treatments, we explored whether possible association between ECT and epilepsy varied with gender and age, or depended on number of treatments and time since last treatment. Since electrode placement has been suggested to influence the risk of adverse effects following ECT [3], we did a supplementary analysis to explore the influence of electrode placement on the risk of developing epilepsy.

Methods

Study population

All citizens in Denmark with a first-time hospital contact (emergency, in- or outpatient) due to an affective disorder between 1st of January 2005 and 31st of December 2015 were included in this cohort study. In total, 175,086 emergency, in- or outpatient hospital patients were identified by record linkage with the Danish National Patient Registry (DNPR) [16] using the International Classification of Diseases version 10 (ICD-10) codes F30.0-F39.9. Main diagnosis at first admission was classified using the following ICD-10 codes: manic episodes (ICD-10:F30), bipolar disorder (ICD-10: F31), single episode depression (ICD-10:F32), recurrent depression (ICD-10:F33), persistent mood disorder (ICD-10: F34), and other or unspecified affective disorders (ICD-10: F38 and F39). DNPR was established in 1977 and holds data on diagnosis, treatments, patient contact types (inpatient, outpatient, or emergency), and dates from all hospital admissions for every patient contact at the individual level. Since 1995, the DNPR has included both somatic and psychiatric patients, as well as outpatient and emergency

contacts, whereas prior to 1995 only inpatient admissions were registered.

A total of 552 individuals with missing information on birth date ($n = 91$), date of death before ($n = 191$) or younger than ten years ($n = 270$) at the time of first hospital contact were excluded from the study. Thus, the study population included 174,534 patients. The study was approved by the Danish Data Protection Agency. According to Danish legislation, approval from the Danish Health Research Ethics Committee System was not required as this study was based purely on register-data.

Measures

Electroconvulsive therapy (Exposure)

From the DNPR we retrieved information on all ECTs registered for patients since 2005. ECT was first registered in Denmark in DNPR from 2003, but the registration was considered complete since 2005 [17]. ECTs were identified by codes provided by the Health Care Classification System (Danish, Sundhedsvæsenets Klassifikations System [SKS]), which is a collection of International, Nordic and Danish classifications. We extracted SKS codes that reflected condition (involuntary or voluntary) and electrode placement (unspecified, unilateral or bilateral). Any treatment with ECT was defined at the time the patient was registered the first time with a relevant SKS-code. We also had information on the number of ECTs and the date for each treatment provided during follow-up.

Epilepsy (Outcome)

In the present study all patients were followed in the DNPR for any epilepsy diagnosis. Incident cases were defined as first emergency, in- or outpatient hospital contact with main or contributory diagnosis of epilepsy (International Classification of Disease (ICD)-10 codes: G40.0-G41.9) from study entry January 2005 until November 2nd, 2016. The validity of epilepsy diagnosis obtained from the DNPR has been assessed in a study of 200 patients admitted between 1977 and 2002 [18]. This showed that 81% of epilepsy diagnoses were confirmed by review of medical records. We identified 5077 with an epilepsy diagnosis registered in the DNPR (ICD-10:G40.0-G40.9 and ICD-8: 345) before study entry, which were excluded. This left 169,457 to be included in the analyses.

We also did a sensitivity analysis combining information on diagnostic codes with data on individual patients' refill of prescriptions for anti-epileptic drugs identified by the Anatomic Therapeutic Chemical (ATC) classification system codes (N03A) in the Danish National Prescription Registry. This register, which was established in 1995, contains information on all prescribed, redeemed drugs sold at Danish pharmacies [19].

Covariables

Level of education, comorbid schizophrenia, previous stroke, antidepressant and antipsychotic medication use have been associated with ECT [1] and risk of epilepsy [20–22], why information on these confounders were included. Data on highest achieved educational level was obtained from the Population's Education register. Individuals educational level was categorized into three groups (low: primary school; middle: high school, vocational education (educations aimed towards manual work), and high: higher education, and higher advanced education). In the DNPR we identified patients with comorbid schizophrenia (ICD-10: F20; ICD-8: 295; 297) or previous stroke diagnosis (ICD-10: I61-I64; ICD-8: 431–434) at study entry.

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