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Medication Use and the Risk of Newly Diagnosed Diabetes in Patients with Epilepsy:
A Data Mining Application on a Healthcare Database

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ABSTRACT

Epilepsy is a common neurological disorder that affects millions of people worldwide. Patients with epilepsy generally require long-term antiepileptic therapy and many of them receive polypharmacy. Certain medications, including older-generation antiepileptic drugs, have been known to predispose patients to developing diabetes. Although data mining techniques have become widely used in healthcare, they have seldom been applied in this clinical problem. Here, the authors used association rule mining to discover drugs or drug combinations that may be associated with newly diagnosed diabetes. Their findings indicate in addition to the most common culprits such as phenytoin and valproic acid, prescriptions containing carbamazepine, oxcarbazepine, or lamotrigine may be related to the development of newly diagnosed diabetes. These mined rules are useful as guidance to both clinical practice and future research.

KEYWORDS

Antiepileptic Drug, Association Rules, Diabetes, Drug-Drug Interaction, Epilepsy

INTRODUCTION

Epilepsy is a common neurological disorder characterized by paroxysmal recurrence of epileptic seizures (Moshé, Perucca, Ryvlin, & Tomson, 2015). Long-term use of one or more antiepileptic drugs (AEDs) to provide optimal seizure control has been the mainstay of treatment for epilepsy (Burakgazi & French, 2016). A survey found that the mean number of AEDs consumed per each patient with epilepsy was 1.7±0.8 (range 1–4) (Eyal, Rasaby, & Ekstein, 2014). In addition, the burden of comorbidities is higher in patients with epilepsy than that in the general population (Keezer, Sisodiya, & Sander, 2016). About 56% of patients with epilepsy were concomitantly treated with at least one other prescription (Eyal et al., 2014). Therefore, prescribers should carefully consider the long-term adverse effects of AEDs—especially of those older-generation AEDs with hepatic enzyme-inducing activities and high potentials for drug-drug interactions (Brodie et al., 2013).

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Prior studies have demonstrated that enzyme-inducing AEDs—such as phenytoin—are associated with markers of elevated vascular risk including increased carotid intima-media thickness (Chuang et al., 2012) and a higher risk of stroke (Hsieh, Lai, Yang, & Lin, 2013). Notably, the prevalence of diabetes is higher in patients with epilepsy (Keezer et al., 2016). It is possible that metabolic side effects of AEDs directly cause diabetes—which, in turn, leads to an increased risk of vascular diseases in patients with epilepsy. For example, phenytoin may cause hyperglycemia through decreased insulin secretion and increased insulin resistance (Fathallah, Slim, Larif, Hmouda, & Ben Salem, 2015). Valproic acid may cause impaired glucose homeostasis, overweight, and metabolic syndrome (Verrotti, Manco, Agostinelli, Coppola, & Chiarelli, 2010). Furthermore, when patients with epilepsy are getting older, the association between AEDs and the increased prevalence of diabetes will become more complicated because of a higher burden of comorbidity (Johnson et al., 2018) and probably because of the cumulative burden of more co-medications. For example, patients with epilepsy have a high risk of psychiatric disorders (e.g. depression) (Keezer et al., 2016), whereas antidepressants may increase the risk of new-onset diabetes (Nguyen, Roussin, Rousseau, Montastruc, & Montastruc, 2018; Siafis & Papazisis, 2018). Therefore, the relationships between AEDs, other co-medications, and the development of diabetes are complex and remain to be elucidated.

Data mining techniques have been used to find undiscovered patterns or to build classification models in many areas including finance and healthcare. The characteristics, large volume, and complexity, of healthcare data have elicited the use of data mining modeling (Koh & Tan, 2005).

The objective of this paper was to analyze the association between drug use in patients with epilepsy and the risk of newly diagnosed diabetes using data mining techniques. By conducting knowledge mining in a huge electronic healthcare database, the research is expected to find the interaction between AEDs and diabetes in the data and to provide reference information to clinicians regarding prescription of AEDs.

The paper unfolds as follows: Section 2 provides a literature summary both of the use of data mining techniques to detect signals of adverse drug reactions and of the application of association rule mining (ARM) to medical data. Section 3 describes the research design and methods. Section 4 presents the findings after data analysis. In Section 5, the results are interpreted and discussed. Contributions to clinical practice as well as limitations and future opportunities of this study conclude the paper.

LITERATURE REVIEW

Data Mining Techniques to Detect Adverse Drug Events

Although traditional pharmacovigilance and reporting systems have been used for decades to detect adverse drug events caused by a marketed drug (Waller, 2006), adverse events of insidious onset—such as of diabetes—may be less likely to be captured by spontaneous reporting systems. Nevertheless, with the build-up of data infrastructure, data mining techniques make the hypothesis-free screening for unsuspected or latent drug-outcome associations feasible; and they help detect signals to complement pharmacovigilance surveillance (Hallas et al., 2018). For example, after mining a reporting system database and electronic medical records of three hospitals in the US, increased blood glucose levels were found to be caused by an unexpected synergistic interaction between paroxetine and pravastatin (Tatonetti et al., 2011). Another example is the detection of a higher risk of hypothyroidism in patients taking some older-generation AEDs (Lai, Yang, Lin, & Hsieh, 2013). However, data mining techniques have rarely been applied to identify potential drug combinations that will cause newly diagnosed diabetes in patients with epilepsy—a vulnerable population in which drug interactions with AEDs are major concerns.

The Transfer Strategy of Digital Information Technology for Heterogeneous Manufacturers

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