Partners in Crime: Kidney Transplantation and Seizure Disorder

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ABSTRACT

Seizure disorder is a common neurologic complication of kidney transplantation and often presents as a complex management challenge. Little is known about the risks mutually conferred by the 2 clinical entities and the effects of such risks on clinical outcomes. Using the National Inpatient Sample, our goal was to examine the effects of kidney transplantation and seizure disorder on mortality, hospitalization statistics, clinical complications, and cost of care. A history of kidney transplantation was shown to negatively affect the care of seizure disorder, and a history of seizure disorder also negatively affected the clinical outcomes of kidney transplantation. Our findings are important for initiating discussions and prompting future studies to further examine disease-specific risks of kidney transplantation.

SOLID ORGAN TRANSPLANTATION (SOT) has changed the lives of millions of patients, with >110,000 transplantations performed annually worldwide [1]. The United States Department of Health and Human Services reported 17,878 kidney transplantations (KTs) nationally in 2015, and there have been >10,000 transplantations performed annually for the last 20 years [2]. Nonetheless, there are significant complications associated with KT, including rejection, perioperative organ failure, infection, metabolic disturbances, medication side effects, and neurologic complications. Advances in perioperative care over the last 2 decades have resulted in significant reductions in mortality and morbidity associated with the procedure. Increased focus has therefore been directed toward the management of postoperative medical conditions and complications. Neuropsychiatric complications, such as seizure, affect more than one-third of all KT recipients and have become one of the main contributors to decreased long-term survival and quality of life [3,4].

Seizure is the second most common neurologic complication among SOT recipients [5] and presents as a complicated management challenge for clinicians. Previous studies have shown a causal link between posttransplant medication and seizures. Specifically, calcineurin inhibitors such as cyclosporine and tacrolimus have been shown to impair reactive oxygen species homeostasis, resulting in vasoconstriction and disruptions in the blood–brain barrier. These agents also have direct toxic effects on oligodendrocytes, inhibiting glutaminergic and γ-aminobutyric acid signaling while depleting serotonin levels [5,6]. Corticosteroid, another medication frequently used in transplant recipients, can lead to epinephrine sensitization and an increased vulnerability to opportunistic central nervous system infections [5], both of which are risk factors for seizure. OKT3 is an immunosuppressant monoclonal antibody targeting CD3 receptors on T cells and has been associated with recurrent seizures due to pro-inflammatory cytokine production and meningeal inflammation [7,8]. Finally, some antibiotics commonly used for surgical prophylaxis, including cephalosporin, are known to lower the seizure threshold [9]. These medication toxicities, as well as other risk factors for seizure including central nervous system infection and cerebrovascular disorder, are all intensified in KT recipients due to disturbances in metabolite homeostasis, toxic material clearance, and circulatory system regulation.

Several studies have shown that seizures are common in SOT recipients, including KT recipients, but there have been few studies suggesting that the care of these patients differs from patients with no history of transplantation [10]. With this in mind, the goal of the present study was to investigate the differences in outcomes among patients admitted for seizures with and without a history of KT. We hypothesized that the unique clinical characteristics of KT

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have a special impact on mortality, length of stay (LOS) in the hospital, cost, and complication risks. Given the predicament of KT recipients with seizures, we next questioned the importance of epileptic status in the initial decision-making process by examining patients admitted for the KT procedure with and without a history of epilepsy. Using a different clinical scenario for this analysis, we hypothesized that a history of epilepsy would negatively affect KT hospitalizations in terms of cost and risks of complications. We believe that the connection between KT and seizure deserves particular attention. An improved understanding of the risks conferred by these 2 clinical entities will provide direction for patient education, preoperative decision-making, postoperative management, and clinical guidelines.

PATIENTS AND METHODS

This study used the National Inpatient Sample (NIS) database from 2002 to 2011, available from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, for our analysis. The NIS is a sample of hospital discharges, representing 20% of all inpatient discharges nationally from nonfederal hospitals in the United States. For all calculations, weights included in the NIS were used to make the estimates nationally representative. All statistical analyses were performed by using Stata version 13.0/MP (Stata Corp, College Station, Tex, United States).

Patients with primary admission diagnoses of seizure disorders were identified by using *International Classification of Diseases, Ninth Revision* (ICD-9), diagnostic codes for epilepsy and recurrent seizures (345). To improve the selectivity of the sample, diagnoses of febrile convulsions (simple), unspecified (780.31), and complex (780.32) febrile convulsions were excluded from the analyses. The selected patients were then separated into 2 groups: KT recipients and others. KT recipients were identified by using diagnostic codes kidney replaced by transplant (V420) and complications of transplanted kidney (996.81).

We examined the impact of KT on epilepsy outcomes, including in-hospital mortality, LOS, hospital charges, and discharge disposition. All charge estimates were adjusted to 2014 US dollars based on inflation rates obtained from the Bureau of Labor Statistics, United States Department of Labor. bivariate and multivariate analyses were performed to delineate the potentially independent modifiers, including age, sex, race, insurance status, hospital size, hospital teaching status, hospital location, hospital region, and preexisting comorbidities. To adjust for the impact of comorbidity on patient outcomes, the Deyo modification of the Charlson Comorbidity Index (CCI) [11] was used as a factor in the models.

To better examine the relationship of seizure disorder and KT between heterogeneous cohorts, a propensity match method was used to generate age- and CCI-matched control subjects at a case vs control ratio of 1:9. Given the prevalence of kidney disease in the KT cohort, the CCI in this context was further modified to exclude chronic kidney disease. Sex was not included as a matching criterion because of nonsignificant differences between the corresponding patient populations, both before and after the matching process. Analyses were then performed on the matched cohorts to determine contributions from factors other than age and coexisting comorbidities.

A separate analysis was devised to examine how a history of epilepsy affects the hospitalization for renal transplantation. Patients undergoing KT procedures were identified by other kidney transplantation (ICD-9 55.69). The ICD-9 diagnostic codes listed in Supplemental Table 1 were used to determine the presence of epileptic disorders. We then compared the demographic characteristics and clinical outcomes of KT hospitalization with and without a history of seizure disorders.

RESULTS

Impact of KT on Seizure Disorder

A total of 232,917 discharges in the NIS database were identified as having primary admission diagnoses of seizure disorders, representing a national patient population of 1,147,719. Of these discharges, 510 had a diagnosis of receiving KT, representing 2508 nationally. Table 1 displays the demographic characteristics for both patient groups according to the NIS national weightings.

Table 1. Demographic Characteristics for Patients Admitted Primarily for an Epileptic Disorder

Characteristic	Patients With Epileptic Disorder Without a History of KT (n = 1,145,165)	Patients With Epileptic Disorder With a History of KT (n = 2508)	*P*
Age category, y			<.0001
<19	23.92	6.90	
19–41	25.53	38.35	
42–57	24.09	32.41	
≥58	26.46	22.34	
Female	49.64	46.24	.21
Race/ethnicity			.08
White	59.20	54.13	
African American	21.68	27.62	
Hispanic	12.46	11.80	
Asian	1.63	2.53	
Native American	0.82	0.24	
Other	4.22	3.68	
Primary payer			<.0001
Medicare	32.13	62.49	
Medicaid	27.22	12.71	
Private	30.55	19.92	
Self-pay	5.67	1.71	
Other	3.77	3.16	
Hospital size			.02
Small	9.35	5.76	
Medium	22.4	20.42	
Large	68.25	73.83	
Hospital region			<.05
Northeast	24.54	21.37	
Midwest	22.13	28.45	
South	35.96	30.99	
West	17.36	19.19	
Urban hospital (vs rural)	91.47	91.69	.88
Teaching hospital (vs nonteaching)	62.19	59.71	.38
Age, y	40.28 ± 0.64	43.33 ± 0.83	<.001
Deyo modification of the Charlson Comorbidity Index	0.86 ± 0.02	3.09 ± 0.07	<.0001

Values are given as % or mean ± standard error.
Abbreviation: KT, kidney transplantation.