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Smoking association with influenza infection in renal transplant recipients

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Abstract

We identified 22 cases of influenza infection among renal transplant recipients and matched them with 66 controls by influenza season to explore risk factors for influenza infection. Active cigarette smoking was associated with influenza infection in this population (adjusted odds ratio 13.1; 95% confidence interval 2.3–76; $P = 0.004$).

Keywords

influenza virus; renal transplant; smoking; organ transplant

Kidneys are the most commonly transplanted solid organ, and the majority of the >160,000 living renal transplant recipients (RTRs) in the United States require chronic immunosuppression to prevent allograft rejection (1). Influenza infection causes considerable morbidity and mortality in RTRs, including increased risk of allograft rejection, pneumonia, sepsis, organ dysfunction, respiratory failure, and death (2–5). Despite recommendations for influenza vaccination in RTRs, questions remain about vaccine efficacy and safety in this population (6). The aim of this study was to investigate novel, and potentially reversible, risk factors of medically attended laboratory-confirmed influenza infection in RTRs.

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Methods

Study design, population, and site

We performed a case-control study within the population of all adult RTRs receiving post-transplant care at Barnes-Jewish Hospital (BJH) in St. Louis, Missouri, a large tertiary-care facility that performs >150 renal transplants annually. Clinical data were collected on RTRs for the study period consisting of the 1999–2000 through 2007–2008 influenza seasons. Human studies approval was obtained through Washington University's Human Research Protection Office.

Definitions

Cases were defined as RTRs age ≥ 18 years with a positive microbiological test for influenza virus, including rapid antigen test, direct fluorescent antibody assay, viral culture, or polymerase chain reaction from nasopharyngeal swabs, sputum, or bronchoscopically-obtained respiratory specimens. Controls consisted of RTRs without acute respiratory illness and were frequency-matched by influenza season in a 3:1 ratio to cases. The date a positive sample was collected defined the date of influenza infection. Cases and controls were required to have sufficient clinical data available during the influenza season. Cigarette smoking status was categorized as active or inactive. Patients not taking immunosuppressive drugs and those with suspected respiratory viral illnesses, defined as having diagnostic testing for respiratory viruses performed during the influenza season of analysis, were not eligible to be controls.

Leukopenia was defined as <3000 white blood cells/mm³, neutropenia was defined as <1000 cells/mm³, and lymphopenia was defined as <300 cells/mm³. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease formula (7). Baseline graft dysfunction was defined as baseline serum creatinine >1.6 g/dL or baseline GFR <50 mL/min/1.73 m². Baseline graft failure was defined as renal replacement therapy (RRT) prior to influenza infection for cases, and RRT prior to the influenza season of analysis for controls. Acute kidney injury was defined as an increase in serum creatinine 1.5 times baseline, decrease in GFR by 25% from baseline, or new requirement of RRT.

Data collection

All RTRs were identified through the Washington University Kidney Translational Research Core (KTRC) database. This database was cross-referenced to a BJH Microbiology Laboratory database of all patients with positive influenza tests within the study period. Controls were selected randomly from the KTRC database. Medical records were reviewed to collect data on demographics, comorbidities, medications, laboratory values, and clinical outcomes. For controls, the most extreme laboratory values and medication exposures within the matched influenza season were used for analysis.

Statistical analysis

Categorical variables were compared by chi-square or Fisher's exact test, as appropriate. Continuous variables were compared by unpaired Student's *t*-test. Continuous variables with a non-normal distribution were log-transformed or were compared by Mann-Whitney *U*-

test. A 2-tailed P -value of <0.05 was considered statistically significant. Multivariate analysis was performed using logistic regression. Variables with P -values of <0.1 by univariate analysis were selected for multivariate analyses. To avoid overfitting, given the small number of cases, regression models were run with 2 variables at a time. The model that minimized Akaike's Information Criterion (AIC) was chosen as the final model. SPSS for Windows version 16.0 was used for all data analyses.

Results

Description of influenza cases

A total of 22 RTRs were identified with laboratory-confirmed influenza infection and were matched by influenza season to 66 controls. Influenza type A accounted for 18 cases and type B accounted for 4 cases. Cases most commonly presented with fever (86%), cough (86%), dyspnea (36%), fatigue (36%), rhinorrhea (21%), sore throat (21%), and myalgias (14%). Four (18%) case patients developed pneumonia. Fourteen cases (64%) were admitted to the hospital, and 2 (9%) were admitted to the intensive care unit. One patient required mechanical ventilation. No cases died during the period of analysis. The median hospital length of stay was 4 days. One case had acute kidney injury requiring initiation of RRT during the hospitalization for influenza infection. Five (23%) cases were treated with antiviral medications: 3 with oseltamivir and 1 each with amantadine and zanamivir. One case with influenza infection was treated for concurrent cytomegalovirus viremia with ganciclovir.

Risk factor analysis

Demographics, comorbidities, and laboratory data for cases and controls, with multivariate analysis are summarized in Table 1. Both groups were similar in regard to gender, age, body mass index, type of transplant, and cytomegalovirus status. Cases were twice as likely as controls to be non-white (50% vs. 24%, $P = 0.023$). Cases were more likely to be a longer time post transplant than controls (median time since transplant 6.7 vs. 5.1 years, respectively, $P = 0.039$). Immunosuppressive regimens were similar between cases and controls (data not shown). Cases were more likely to be active cigarette smokers. Six cases (27%) were identified as active smokers compared with only 2 (3%) controls ($P = 0.003$). Chronic obstructive pulmonary disease was not statistically more common among cases, although 3 cases (14%) and 2 controls (3%, $P = 0.097$) had this diagnosis.

Laboratory values were similar between cases and controls. Two cases and 3 controls were on RRT before the analyzed influenza season, but remained on immunosuppressive medications, so were included in the study. One case and 1 control had new requirement for RRT during the analyzed influenza season. Rates of graft failure and dysfunction were not significantly different between cases and controls.

BJH recommends influenza vaccination for all RTRs. However, accurate data on influenza vaccine receipt data were limited. Vaccination status was confirmed for only 4 (18%) cases (3 received, 1 did not) and 5 (8%) controls (all received).

Logistic regression models were performed with 2 variables at a time for variables with P -values <0.1 in univariate analysis. All considered models included active smoking. Other variables considered were non-white race, time since transplant, chronic obstructive pulmonary disease, and coronary artery disease. Active smoking was statistically significant in every model with the lower bounds of all 95% confidence intervals (CI) >1 . The adjusted odds ratios (aOR) for active smoking in these models ranged from 10.2 to 14.0. The model with smoking and non-white race had the lowest AIC, so was chosen as the final multivariate model. In this model, active smoking had an aOR of 13.1 (95% CI 2.3–76, $P=0.004$) and non-white race had an aOR of 3.4 (95% CI 1.1–10, $P=0.028$).

Discussion

This case-control study provides further evidence that medically-attended laboratory-confirmed influenza infection is associated with substantial morbidity in RTRs, as evidenced by moderate rates of hospitalization, care in intensive care unit, and mechanical ventilation (5). Novel to this study is the identification of active smoking as a potential risk factor for influenza virus infection within this study population.

Smokers have been demonstrated to have a higher rate of influenza infection owing to many mechanisms involving weakened respiratory defenses (8–10). A recent study showed that T-lymphocytes are more readily activated in the nasal mucosa of non-smokers compared with smokers (11). It has been suggested that smokers have both increased susceptibility and increased severity of infections, including influenza and pneumonia (12). Prior studies concerning smoking and RTRs use smoking as a marker of non-adherence and as a risk factor for graft dysfunction (13, 14). To our knowledge, no other study has explored smoking as a risk factor for influenza infection in RTRs.

A strength of this study is that all cases were microbiologically confirmed to have influenza infection. However, this stringent case ascertainment method resulted in relatively few cases. Influenza infections that were mild, treated empirically, or treated by outside providers may not have been detected. The study design identified cases likely to be clinically severe and requiring attention by transplant physicians. The high number of perioperative controls, although not statistically significant, may have biased time-since-transplant value to be lower for controls. Although RTRs may be less likely to smoke just after transplantation, active smoking remained significant after adjusting for time since transplant. Vaccination status between cases and controls cannot be compared owing to inadequate data. Despite guidelines by the American Transplantation Society recommending annual influenza vaccination for all solid organ transplant recipients, nearly half of those eligible remain unvaccinated (6, 15), possibly because of concerns regarding vaccine-elicited anti-human leukocyte antigen antibodies (16). Although limitations in the study design must be considered when interpreting the results, the magnitude of the effect of active smoking on influenza infection supports a true association.

Our study reinforces existing literature that influenza is a serious health concern for RTRs and suggests that active smoking is a risk factor for influenza infection in this population. RTRs should continue to be counseled about smoking cessation and receiving influenza

vaccinations. Prospective studies are warranted to further examine the impact of smoking on influenza infection.

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Abbreviations

RTRs	renal transplant recipients
BJH	Barnes-Jewish Hospital
GFR	glomerular filtration rate
RRT	renal replacement therapy
KTRC	Washington University Kidney Translational Research Core
AIC	Akaike's Information Criterion
CI	confidence interval
aOR	adjusted odds ratio

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Table 1

Demographics, comorbidities, and laboratory values (A) of influenza-infected renal transplant cases ($n=22$) and matched controls ($n=66$), with (B) final multivariate model with odds ratio and 95% confidence interval estimates

A. Characteristics	Cases ($n=22$)	Controls ($n=66$)	P-value
Demographics			
Gender, female (%)	8 (36)	31 (47)	0.386
Race			
White (%)	11 (50)	50 (76)	
Non-white (%)	11 (50)	16 (24)	0.023
Age at influenza in years, mean (range)	51 (25–82)	50 (23–70)	0.740
Time since transplant in years, median (range)	6.7 (0–14)	5.1 (0–24)	0.039
Transplant within 30 days of admission (%)	1 (5)	9 (14)	0.440
Transplant type			
Living related (%)	6 (27)	26 (39)	0.306
Living unrelated (%)	1 (5)	4 (6)	
Cadaveric (%)	14 (64)	36 (55)	0.456
Unknown (%)	1 (5)	0 (0)	
CMV mismatch (D+/R–) (%)	8 (36)	12 (18)	0.088
Baseline graft dysfunction (%)	9 (41)	24 (36)	0.801
Baseline graft failure (%)	2 (9)	3 (5)	0.595
BMI, mean (kg/m ²)	28.4	27.7	0.747
BMI >30 kg/m ² (%)	5 (36)	9 (32)	0.326
Comorbidities			
Smoking, active (%)	6 (27)	2 (3)	0.003
COPD (%)	3 (14)	2 (3)	0.097
CAD (%)	6 (27)	6 (9)	0.066
CHF (%)	1 (5)	2 (3)	1
Diabetes mellitus (%)	8 (36)	20 (30)	0.597
Laboratory values			
Creatinine, mean (mg/dL)	3.2	2.6	0.55
GFR, mean (mL/min/1.73 m ²)	40	43	0.769
WBC (10 ³ /mm ³)	6.6	6.0	0.323
Neutropenia (%)	1 (2)	2 (4)	1
Lymphopenia (%)	4 (18)	6 (9)	0.72
B. Multivariate analysis			
	aOR	95% CI	P- value
Active smoking	13.1	2.3–76	0.004
Non-white race	3.4	1.1–10.1	0.028

Bold values are significant.

CMV, cytomegalovirus; D, donor; R, recipient; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; GFR, glomerular filtration rate; WBC, white blood cell count; aOR, adjusted odds ratio; CI, confidence interval.