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Transplant and risk of Parkinson disease

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ABSTRACT

Introduction: The pathophysiology of Parkinson's disease (PD) remains unclear, but growing evidence supports a role of neuroinflammation. The purpose of this study was to investigate the association between tissue transplantation and PD risk, given the importance of immunosuppressants in post-transplant management.
Methods: We performed a case-control study among Medicare beneficiaries age 66–90 using claims from 2004 to 2009. We used International Classification of Diseases, Ninth Edition (ICD-9) and Current Procedural Terminology (CPT) codes to identify PD (89,790 incident cases, 118,095 population-based controls) and history of tissue transplant (kidney, heart, liver, lung, and bone marrow). We investigated risk of PD in relation to tissue transplant in logistic regression models, adjusting for age, sex, race, smoking, and overall use of medical care.
Results: Beneficiaries who had received a tissue transplant at least five years prior to PD diagnosis or reference had a lower risk of PD (odds ratio [OR] 0.63, 95% confidence interval [CI] 0.53, 0.75) than those without tissue transplant. This inverse association was observed for kidney (OR 0.63, 95% CI 0.47, 0.84), heart (OR 0.58, 95% CI 0.40, 0.83), lung (OR 0.41, 95% CI 0.21, 0.77), and bone marrow (OR 0.57, 95% 0.38, 0.85) transplants. Associations were attenuated, but remained, following adjustment for indications for the respective type of transplant. Liver transplant was not associated with PD risk.
Conclusions: Patients undergoing tissue transplant may have a lower risk of developing PD than the general population. Further studies are needed to determine if this association is causal and if immunosuppressants mediate this association.

1. Introduction

With the growing prevalence and economic impact of Parkinson's disease (PD) [1], there is an urgent need to understand the pathophysiology of PD, in order to identify effective strategies for prevention and treatment. There is a growing body of evidence that neuroinflammation may play a role in disease risk and progression [2,3]. Prior studies have demonstrated reactive microglia in the basal ganglia and complement proteins in the substantia nigra in patients with PD and higher levels of inflammatory cytokines in the substantia nigra, cerebrospinal fluid, and peripheral blood of those with PD in comparison with controls [4–7]. In addition, genes related to allergy or underlying defects in the immune system have been implicated in PD [8,9]. Because inflammation may play a role in the pathophysiology of PD, it is possible that immunosuppressants could reduce the risk of PD. In fact, we recently demonstrated that those taking selected immunosuppressants had a lower risk of PD than the general Medicare population [10].

We recently developed a predictive model to identify people with PD using medical claims data during their five-year prodromal period [11]. Codes associated with PD, after adjustment for covariates and rigorous correction for multiple comparisons, were used to develop the model. One category of disease associated with PD in this initial step was solid organ transplantation. Immunosuppressant medications are used commonly long-term in patients who have undergone tissue transplantation; these medications have unique mechanisms, which ultimately reduce inflammation systemically, including within the central nervous system. Because the inverse association between tissue transplantation and PD could have important implications for primary prevention of PD or neuroprotection in established PD patients, we sought to follow-up these findings with a focused investigation of the risk of PD in relation to tissue transplant.

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2. Methods

2.1. Study design and eligibility criteria

The Centers for Medicare and Medicaid Services (CMS) and the Washington University Human Research Protection Office approved this case-control study using de-identified Medicare claims data. Medicare is the federal health insurance for the United States (U.S.) and provides comprehensive medical insurance coverage for those 65 and older, and certain younger people with disabilities and selected medical conditions. Medicare covers the cost of hospital care (Medicare Part A), physician services and medical supplies (Medicare Part B), and prescription coverage for an additional fee (Medicare Part D). Medicare covers 80% of "Medicare allowable expenses," and patients either pay for the remainder of the cost out of pocket or use a secondary, private insurance. Approximately 50% of Medicare eligible patients use a Medicare Advantage plan (Medicare Part C) for their health insurance. These plans do not report health care claims to CMS; therefore, Part C participants cannot be included in Medicare administrative data studies. Researchers can purchase from CMS administrative claims data, excluding all identifying information such as name, address, and social security number. We used the 2009 beneficiary annual summary file (BASF) to obtain demographic data, identify all potential subjects, and evaluate study eligibility. All beneficiaries included were age-eligible for Medicare by January 1, 2007 (born by February 1, 1942), i.e. age 66 years and 11 months or older at PD case diagnosis or control reference date in 2009. All cases and controls also met the following criteria in 2009: Medicare Parts A or B coverage; no Medicare Advantage plan (Part C) coverage; U.S. residence; and age ≤ 90 at year-end (or death in 2009 after diagnosis/reference). For each case and control in this study, we obtained comprehensive Medicare Part A and B claims data that included all carrier (physician/supplier Part B), outpatient, inpatient, skilled nursing facility, durable medical equipment, and home health care claims from 2004 to 2009.

2.2. Data sharing

Under a Data Use Agreement, CMS prohibits data sharing of Medicare data. Only CMS approved co-investigators are permitted to access these data.

2.3. PD case identification and control selection

Incident PD cases were identified using International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9) diagnosis codes in these claims data; all had at least one ICD-9 code for PD (332 or 332.0) in 2009, but no prior year. We excluded cases whose PD case status was uncertain, as previously described [11], including if they had an ICD-9 code for Lewy body dementia or atypical parkinsonism (ICD-9 331.82 or 333.0 in any year). Of all eligible 2009 beneficiaries, 89,790 had incident PD, met the above study criteria, and thus were included in the present study as cases. (Fig. 1).

For controls, we selected a 0.5% random sample of all potential beneficiaries, who had no ICD-9 code for PD in 2004 to 2009 and met the same eligibility criteria as PD cases, as detailed above, but who had no prior codes for PD, atypical parkinsonism, or dementia with Lewy bodies. To identify these controls and select randomly from them, we used the 2009 Medicare base file (BASF). We first enumerated all potential controls eligible for this study. We then used a random number generator to assign each potential control a random number (continuous) and a random Julian date (integer) within 2009 for use as a control reference date. We then selected a 0.5% random sample of all potential controls eligible for the present case-control study by identifying those who had the lowest random numbers and who were still alive on their randomly assigned reference date. Matching was not performed so that model coefficients for known PD risk factors could be included in a predictive model of PD, the primary purpose of obtaining the present case-control sample [11]. In total, we included 118,095 controls in the present study. (Fig. 1).

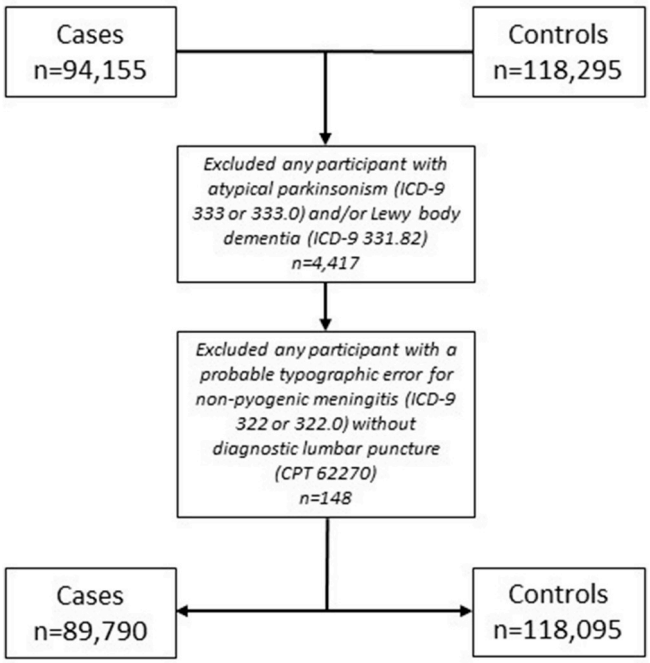

Fig. 1. Diagram of study selection and exclusions.

2.4. Ascertainment of tissue transplant

We used the complete claims data from 2004 to 2009 to identify cases and controls with a history of tissue transplant. We defined history of tissue transplant as any beneficiary with an ICD-9 "V code" that indicated transplantation of a tissue, i.e. kidney (V42.0), heart (V42.2), lung (V42.6), liver (V42.7), pancreas (V42.83), or history of transplant of bone marrow and/or peripheral stem cells (V42.81 and/or V42.82) any time in 2004 to 2009 prior to PD diagnosis/control reference. In addition we required that there be no evidence that the transplant had occurred during the period for which we had claims data (during the five years prior to PD diagnosis/control selection) when symptoms of prodromal PD, such as dementia, could affect whether a beneficiary was eligible for a tissue transplant. Specifically, regardless of the above V codes, we considered as not exposed any beneficiary who had an ICD-9 diagnosis, ICD-9 procedure code, or a Current Procedural Terminology (CPT) code indicating that they had undergone or had been awaiting a transplant during the 2004 to 2009 period. We focused on organ transplant, since the initial step of our predictive model development indicated that solid organ transplant codes were inversely associated with PD. However, for comparison, we assessed, using the same methods as above, history of cornea transplant (ICD-9 V42.5).

2.5. Statistical analysis

Statistical analyses were performed using Stata SE 13.1 software (StataCorp, College Station, TX). We adjusted for covariates known to be associated with PD (age, sex, race/ethnicity, smoking) in the logistic regression models with PD as the outcome and tissue transplant as the independent variable. Age was coded as two linear splines, with a knot at age 85, since the relationship between age and PD risk in our data was best modeled by two separate lines with different slopes. Race/ethnicity was coded as a dichotomous variable (non-Hispanic white vs. other/unknown). We adjusted for smoking by including in all models the predicted probability of "ever" tobacco use as a continuous variable,

Table 1
Characteristics of incident Parkinson's disease (PD) cases and controls, Medicare 2009.

	PD Cases N = 89,790, n (%)	Controls N = 118,095, n (%)	Unadjusted OR (95% CI)[a]	Mutually adjusted OR (95% CI)[a]
Age, years				
66-69	7,230 (8.1)	21,613 (18.3)	1.0 (reference)	1.0 (reference)
70-74	17,522 (19.5)	34,180 (28.9)	1.53 (1.48, 1.58)	1.48 (1.43, 1.53)
75-79	22,304 (24.8)	26,511 (22.4)	2.51 (2.44, 2.60)	2.33 (2.26, 2.41)
80-84	24,150 (26.9)	21,494 (18.2)	3.36 (3.25, 3.47)	2.99 (2.90, 3.09)
85-90	18,584 (20.7)	14,297 (12.1)	3.89 (3.75, 4.02)	3.37 (3.26, 3.49)
Overall Mean (SD)	78.8 (6.1)	76.0 (6.2)	1.074 (1.072, 1.075)	–
Female	45,106 (50.2)	67,358 (57.0)	0.76 (0.75, 0.77)	0.57 (0.56, 0.58)
Race/ethnicity				
White	79,697 (88.8)	102,071 (86.4)	1.0 (reference)	1.0 (reference)
Black	5,386 (6.0)	8,893 (7.5)	0.78 (0.75, 0.80)	0.83 (0.80, 0.86)
Pacific Islander/Other	872 (1.0)	1,786 (1.5)	0.63 (0.58, 0.68)	0.68 (0.63, 0.74)
Asian	1,565 (1.7)	2,558 (2.2)	0.78 (0.74, 0.83)	0.73 (0.69, 0.78)
Hispanic	1,904 (2.1)	2,194 (1.9)	1.11 (1.04, 1.18)	0.98 (0.92, 1.05)
Native American	285 (0.3)	484 (0.4)	0.75 (0.65, 0.87)	0.85 (0.73, 0.99)
Unknown	81 (0.1)	109 (0.1)	0.95 (0.71, 1.27)	0.88 (0.66, 1.19)
Smoking Index[b]				
Index ≥ Median	38,492 (42.9)	65,451 (55.4)	0.60 (0.59, 0.61)	0.57 (0.56, 0.59)

[a] Odds ratio and 95% confidence interval; mutually adjusted means adjusted for all other covariates with an OR in the column.
[b] Predicted probability of ever smoking divided by the person's total number of unique diagnosis codes (or one for 292 cases and 6,227 controls without any diagnosis codes).

which we have validated previously, and ever/never oxygen use, as previously, as a dichotomous indicator of greater probability of smoking and greater duration and intensity of smoking [11–13]. We also adjusted *a priori* for the total number of unique diagnosis codes as a continuous variable as an overall indicator of use of medical care that is associated with diagnosis of PD [14].

We repeated analyses while considering the type of tissue transplant, when sufficiently common, i.e. kidney, heart, lung, liver, and bone marrow/stem cell. In these models, we examined the effect of adjusting for the potential causes of the respective type of transplants, i.e. confounding by indication (see footnotes in Table 2 for the respective indications and ICD-9 codes). We also examined the effect of adjusting for high alcohol use, which we inferred using selected ICD-9 codes, as previously [15]. We did not adjust for this variable *a priori* because these codes are uncommonly recorded (1.1% cases, 0.61% controls). For all models, statistical significance was assessed as two-sided $p < 0.05$, as evidenced by a 95% CI that excluded one.

3. Results

As expected, patients with PD tended to be older than controls (mean 78.8 vs. 76.0 years), and were more likely to be male (49.2% vs. 43.0%) and white (88.8% vs. 86.4%) (Table 1). In the five years prior to diagnosis, PD cases used more medical care, on average, than controls, as measured by total count of unique ICD-9 codes. After accounting for this greater use of medical care, PD cases were, as observed previously [11], less likely to smoke than controls (Table 1).

Overall, patients who had undergone tissue transplant more than five years prior to PD diagnosis or reference had lower risk of PD (OR 0.63, 95% CI 0.53, 0.75) (Table 2). Kidney transplant (OR 0.63, 95% CI 0.47, 0.84), heart transplant (OR 0.58, 95% CI 0.40, 0.83), and lung transplant (OR 0.41, 95% CI 0.21, 0.77) were each associated with lower risk of PD. Liver transplant was not associated with risk of PD (OR 0.89, 95% CI 0.56, 1.42) (Table 2). Adjustment for high alcohol use did not materially alter this association (OR 0.87, 95% CI 0.55, 1.37, not shown in table), nor for other transplants. Corneal transplant also was not associated with PD risk (OR 0.88, 95% CI 0.71, 1.09, not shown in table). However, as for most organ transplants, risk of PD was inversely associated with history of bone marrow/peripheral stem cell transplant (OR 0.57, 95% 0.38, 0.85) (Table 2).

To examine consistency of results, we analyzed the risk of PD by medical etiology in each of the most common tissue transplant categories (Table 2). Results did not vary markedly by underlying cause of transplant. Of the various causes of kidney transplant, kidney transplant due to hypertension with end-stage renal disease, diabetes mellitus with renal complications, and especially glomerulonephritis were associated with lower risk of PD. Heart transplant due to all common causes, i.e. coronary artery disease (CAD)/ischemic cardiomyopathy, valvular disease, and nonischemic cardiomyopathy was associated with lower risk of PD.

When we adjusted for the various potential underlying causes of tissue transplant, tissue transplant overall (as well as kidney, heart, lung, and bone marrow/stem cell transplants) was still associated with a lower risk of PD, although the association for kidney transplant was no longer significant (Table 2). In addition, we observed that most of the underlying conditions were also inversely associated with PD, but not nearly as strongly as having a tissue transplant, with ORs for the conditions closer to null (Table 3).

4. Discussion

This study demonstrates a strong inverse association between tissue transplant and risk of PD. These findings were consistent across nearly all types of tissue transplant, including kidney, heart, lung, and bone

Table 2
History of tissue transplant[a] and risk of PD, overall and by tissue and underlying cause of transplant,[b] Medicare 2009.

	PD Cases N = 89,790, n	Controls N = 118,095, n	OR (95% CI)[c]
Tissue transplant[a]	278	302	0.63 (0.53, 0.75)
All tissue transplants, adjusted for all known causes[b]			0.70 (0.59, 0.84)
Kidney transplant[a,d]	109	108	0.63 (0.47, 0.84)
Hypertension with end-stage renal disease	76	60	0.66 (0.45, 0.95)
Diabetes mellitus with renal complications	55	43	0.60 (0.39, 0.93)
Glomerulonephritis	18	20	0.34 (0.17, 0.68)
Other[d]	17	12	0.70 (0.30, 1.61)
Unknown	25	31	0.76 (0.43, 1.32)
All kidney transplants, adjusted for all known causes[b]			0.75 (0.56, 1.01)
Heart transplant[a,e]	64	72	0.58 (0.40, 0.83)
CAD/ischemic cardiomyopathy	54	54	0.58 (0.39, 0.88)
Valvular disease	48	43	0.61 (0.39, 0.95)
Nonischemic cardiomyopathy	21	31	0.36 (0.20, 0.66)
Other/unknown[e]	22	12	0.68 (0.32, 1.45)
All heart transplants, adjusted for all known causes[b]			0.61 (0.42, 0.88)
Liver transplant[a,f]	47	42	0.89 (0.56, 1.42)
Nonalcoholic fatty liver disease	11	11	0.73 (0.31, 1.74)
Chronic viral/infectious hepatitis	16	12	1.02 (0.45, 2.32)
Alcoholic or drug-induced liver injury	17	11	1.16 (0.50, 2.70)
Other[f]	20	21	0.68 (0.34, 1.35)
Unknown	20	16	0.99 (0.48, 2.04)
All liver transplants, adjusted for all known causes[b]			0.97 (0.61, 1.54)
Lung transplant[a,g]	18	29	0.41 (0.21, 0.77)
All lung transplants, adjusted for all known causes[b,h]			0.42 (0.22, 0.80)
Bone marrow/stem cell transplant[i]	54	66	0.57 (0.38, 0.85)
All bone marrow/stem cell transplants, adjusted for all known causes[b,h]			0.62 (0.42, 0.93)

Abbreviations: OR = Odds ratio, CI = Confidence Interval, CAD = Coronary artery disease.

[a] History of kidney, heart, liver, lung, pancreas, bone marrow, or stem cell transplant, with five year exposure lagging, i.e. presence of the respective ICD-9 V42.x code in 2004–2009 prior to PD diagnosis/control reference, and an absence of any diagnosis or procedure code in the same period that indicated that any transplant occurred during this five year period. These include the respective ICD-9 procedure codes, respective CPT codes, codes for transplant of unspecified organ type; first month pharmacy pack for immunosuppression following transplant; or awaiting transplant status during this period. Pancreas not shown due to small numbers. Other solid organs are not included because no specific ICD-9 V42 code exists for specific solid organ transplants other than the ones listed above.

[b] Potential underlying cause of transplant and other relevant comorbidities as detailed in supplemental table. Numbers may exceed the total within a type of transplant due to multiple underlying comorbidities.

[c] Odds ratio and 95% confidence interval, adjusted for age (continuous), sex, race/ethnicity, smoking (oxygen use and predicted probability of ever tobacco smoking), and total number of unique diagnosis codes; and where noted additionally adjusted for all known causes of the respective type(s) of transplant.

[d] ICD-9 V42.0. Other causes of kidney transplant (polycystic kidney disease, rheumatologic causes, and vascular causes) were combined due to small numbers.

[e] ICD-9 V42.1. Other causes of heart transplant (congenital heart disease, and hypertension complicated by heart failure) were combined due to small numbers. Causes were unknown for 13 subjects.

[f] ICD-9 V42.7. Other causes of liver transplant (biliary, neoplastic, and metabolic or genetic) were combined due to small numbers.

[g] ICD-9 V42.6.

[h] Not analyzed by cause due to small sample sizes.

[i] ICD-9 V42.81 and/or V42.82.

marrow. Important strengths of this study are that all transplant diagnostic codes investigated occurred prior to the diagnosis of PD and that we excluded any transplants that occurred during the five-year prodromal PD phase or respective period among controls. In those who received tissue transplant, most of the causes of tissue transplant, such as vascular disease and diabetes were associated with lower risk of PD,

Table 3
Tissue transplant risk factors and risk of Parkinson's disease (PD) among all beneficiaries without tissue transplant,[1] Medicare 2009.

	PD Cases N = 89,512,[a] %	Controls N = 117,793,[a] %	OR (95% CI)[b]
Kidney transplant causes[c]			
Hypertension with end stage renal disease	5.5	3.2	0.76 (0.73, 0.80)
Diabetes mellitus with renal complications	5.5	3.3	0.87 (0.83, 0.91)
Glomerulonephritis	1.5	0.9	0.81 (0.74, 0.88)
Other			
Rheumatologic	1.4	1.0	0.93 (0.85, 1.01)
Vascular	0.5	0.3	0.73 (0.63, 0.86)
Polycystic kidney disease	0.2	0.1	0.79 (0.63, 1.00)
Heart transplant causes[c]			
CAD/ischemic cardiomyopathy	58.8	41.6	0.97 (0.95, 0.99)
Valvular disease	41.4	28.6	0.89 (0.87, 0.91)
Nonischemic cardiomyopathy	12.4	8.2	0.81 (0.78, 0.83)
Other			
Congenital heart disease	7.6	4.7	0.87 (0.84, 0.91)
Hypertension with heart failure	6.2	3.4	0.91 (0.86, 0.95)
Liver transplant causes[c]			
Nonalcoholic fatty liver disease	3.7	3.0	0.84 (0.79, 0.88)
Chronic viral/infectious hepatitis	0.9	0.7	0.95 (0.85, 1.06)
Alcoholic or drug-induced liver injury			
Drug-induced	2.8	1.9	0.91 (0.86, 0.97)
Alcoholic	0.5	0.4	1.07 (0.92, 1.23)
Other			
Neoplastic	1.7	1.3	0.82 (0.76, 0.89)
Acute liver failure	1.3	0.8	0.95 (0.87, 1.05)
Biliary	0.6	0.4	0.71 (0.62, 0.81)
Lung transplant causes[c]			
COPD	30.6	22.2	0.93 (0.91, 0.96)
Primary pulmonary hypertension	3.2	2.1	0.78 (0.74, 0.83)
Bronchiectasis	1.9	1.3	0.78 (0.72, 0.84)
Idiopathic pulmonary fibrosis	0.8	0.6	0.77 (0.69, 0.86)
Bone marrow/stem cell transplant causes[c]			
Myeloproliferative disorders	2.3	1.5	0.93 (0.87, 1.00)
Cancers of the blood-forming organs/hematopoietic neoplasms			
Leukemia	1.1	0.8	0.80 (0.72, 0.88)
Multiple myeloma	1.0	0.6	1.00 (0.90, 1.11)
Lymphoma	0.8	0.6	0.71 (0.64, 0.80)
Anemia			
Severe aplastic anemia	1.1	0.6	0.91 (0.82, 1.01)
Thalassemia	0.2	0.2	0.91 (0.73, 1.14)
Sickle cell disease	0.04	0.04	0.63 (0.40, 1.01)
Other			
Metabolic syndromes	0.9	0.6	1.09 (0.98, 1.21)
Immune deficiencies	0.4	0.2	1.14 (0.95, 1.37)
Paroxysmal nocturnal hemoglobinuria	0.1	0.03	0.94 (0.59, 1.49)
Hemophagocytic lymphohistiocytosis	0.02	0.01	0.66 (0.30, 1.47)

Abbreviations: OR = Odds ratio, CI = Confidence Interval, CAD = Coronary artery disease, COPD = Chronic obstructive pulmonary disease.

[a] Excludes all subjects (278 cases, 302 controls) who received tissue transplant defined in Table 2; number of Medicare beneficiaries may not add up to total due to beneficiaries in multiple categories.

[b] Odds ratio and 95% confidence interval, adjusted for age (continuous), sex, race/ethnicity, smoking (oxygen use and predicted probability of ever tobacco smoking), and total number of unique diagnosis codes.

[c] ICD-9 diagnostic and procedure codes detailed in supplemental table.

consistent with our recent predictive model study [11]. These associations are in contrast to other studies which indicate a higher risk of PD in those with diabetes [16] and viral hepatitis [17]. Our ORs were generally lower, even for cardiovascular disease [18], likely due to our more aggressive adjustment for use of medical care [14]. However, the lower risk of PD in relation to most tissue transplant categories largely remained even after adjusting for these indications, demonstrating that these findings are not likely to be due entirely to confounding by

indication. Nevertheless, some confounding may persist given our reliance on five years of claims data. We also cannot rule out the possibility of residual confounding by use of tobacco, alcohol, or IV drugs. Overall, this study provides potential evidence of a specific, but unknown, neuroprotective effect of tissue transplant.

One potential interpretation of our results is that immunosuppressants may lower risk of PD, as suggested previously [10,19]. Supporting this hypothesis are both the observations of a consistent protective effect against PD across several categories of solid organ transplantation as well as bone marrow/peripheral stem cell transplant, even though the end-stage organ mechanisms are quite distinct. We speculate that the common mechanism may be treatment with immunosuppressants, which is standard of care for organ and bone marrow transplantation, in contrast to corneal transplantation in which immunosuppressant use is less common [20]. Studies have shown that the use of agents with anti-inflammatory properties are neuroprotective in animal models of PD [21,22] and may be associated with a lower risk of PD, most notably, nonsteroidal anti-inflammatory drugs (NSAIDs) [23,24]. On the other hand, although initial reports suggested that vitamin E were associated with a reduced risk of PD [25], a pivotal clinical trial failed to demonstrate any impact of vitamin E on disease progression in early stage PD patients [26] or on development of disease complications. Similarly, while early studies suggested that the antioxidant coenzyme Q may slow functional decline in PD patients [27–29], coenzyme Q supplementation failed to slow progression of PD in a critical study in early PD patients [30]. The inconsistency between pre-clinical models and human clinical trials may be due to the limitations of lesion-based PD models such as MPTP [31] and 6-hydroxydopamine [32] or non-specific anti-inflammatory mechanisms. Recently, data from rigorously designed epidemiology studies have led to clinical trials based upon novel mechanisms, most notably urate modification [33]. If our hypothesis is correct, and immunosuppressant use in the setting of tissue transplantation reduces risk of PD, many of these therapies bind to specific receptors, which may provide a more targeted neuroprotective effect against PD.

As with any study, there are several important limitations. While our overall sample size was very large, the number of patients in the sub-categories of tissue transplantation were considerably smaller. Another important limitation of any study using Medicare claims data is the necessary restriction of subjects to those age 65 and older. Confirmation in another population-based study or in a longitudinal cohort study, that include a wider age range, will be essential to further our understanding between tissue transplant and PD. Most of the Medicare beneficiaries with tissue transplants in our study had the transplant prior to obtaining Medicare coverage, limiting our ability to conduct longitudinal analysis using time to PD diagnosis as the outcome [34]. Ideally, we would have investigated whether specific immunosuppressants mediated these associations, but, unfortunately, we did not have sufficient Medicare Part D prescription medication data. Future studies with more recent Medicare data will be needed. While it is possible that other characteristics of prodromal PD patients with end-stage organ failure precluded organ transplantation, the PD patients included in our study were all in their prodromal phase and did not carry a PD diagnosis, which could potentially affect physician willingness to subject them to the rigors of a transplant. Our study is also limited by how physicians and their staff code for transplant, various comorbidities, and PD, since the primary purpose of Medicare claims is to reimburse providers and hospitals for services rendered. Nevertheless, we identify all known risk factors for PD in this case-control dataset [11] and the temporal pattern of prodromal disease evolution [35–38] are remarkably similar to clinical experience.

5. Conclusion

This study provides evidence that tissue transplant may be associated with a lower PD risk, warranting further investigation to identify factors that mediate this relationship, including a potential effect of immunosuppressive therapy on PD risk.

Authors' roles

Jessica Fan, MD performed data analysis and created the initial draft of this manuscript.

Susan Searles Nielsen, PhD and Irene M. Faust, MPH performed data analysis and provided critical edits to this manuscript.

Brad A. Racette, MD obtained study funding, formulated the study hypothesis and design, and provided critical edits to this manuscript.

All authors have approved the final article.

Conflicts of interest

None.

Data accessibility

Data sharing of Medicare data is prohibited is by the Centers for Medicare and Medicaid Services under a Data Use Agreement. Only the co-authors are permitted to access these data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.013.

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