The incidence rates and risk factors of Parkinson disease in patients with psoriasis: A nationwide population-based cohort study

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Background: The association between psoriasis and Parkinson disease has not been established.

Objective: To determine the incidence rates and risk factors of Parkinson disease in patients with psoriasis.

Methods: We conducted a nationwide population-based cohort study. The data from patients with psoriasis (N = 548,327, ≥20 years of age, 53.32% men and 46.68% women) and age- and sex-matched control patients (N = 2,741,635) without psoriasis were analyzed in this study.

Results: The incidence rates of Parkinson disease per 1000 person-years were 0.673 and 0.768 in the control and psoriasis groups, respectively. The psoriasis group showed a significantly increased risk of developing Parkinson disease (hazard ratio [HR] 1.091, 95% confidence interval [CI] 1.029-1.115). The risk of Parkinson disease was significantly higher among the psoriasis patients who were not receiving systemic therapy (HR 1.093, 95% CI 1.031-1.159) and lower among the psoriasis patients on systemic therapy (HR 1.04, 95% CI 0.806-1.316).

Limitations: The limitations of this study included the retrospective design, patient inclusion solely on the basis of diagnostic codes, and unavailability of data on confounding factors.

Conclusion: Systemic anti-inflammatory agents might mitigate the risk of Parkinson disease in psoriasis patients. (J Am Acad Dermatol 2020;83:1688-95.)

Key words: cohort study; incidence; Parkinson disease; population-based; psoriasis; risk factor.

Parkinson disease (PD) is a common neurodegenerative disease characterized by resting tremor, bradykinesia, rigidity, or postural imbalance. It can also present with nonmotor symptoms, such as dementia and depression.[1,2] The prevalence of PD is generally estimated to be 0.3% in the total population and about 1% among adults >60 years of age.[3] PD, like Alzheimer disease, can increase the social and economic burdens of an aging society. Although genetic studies of PD are being conducted, the underlying mechanism of the disease remains unclear. Mitochondrial dysfunction, oxidative stress, and mishandling of proteins have been proposed as major mechanisms involved in the pathogenesis of PD.[4] The risk factors for PD include pesticides, herbicides, heavy metals, and smoking. A previous study has reported an increased risk of PD in patients with some autoimmune disorders, such as thyroid disease, pernicious anemia, and multiple sclerosis.[1]

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Psoriasis is a chronic inflammatory skin disorder that affects 2%-4% of the general population; however, local differences in the prevalence of psoriasis have been observed.[5-7] T_H1 and T_H17 cell–related immunologic imbalances as well as genetics play a role in the pathogenesis of this disease.[5] The lifestyle factors drinking, smoking, and obesity are considered independent risk factors for psoriasis.[8,9] Treatment of psoriasis includes topical and systemic treatments. Systemic therapy with conventional agents, such as acitretin, cyclosporine, and methotrexate, as well as biologics targeting specific pathogenesis, is used if the disease is not controlled by topical therapy.[7]

Sheu et al showed an increased risk of PD in 4885 Taiwanese patients with psoriasis,[10] and a meta-analysis by Ungprasert et al also demonstrated an association between psoriasis and PD.[11] In addition, the use of nonsteroidal anti-inflammatory drugs was shown to decrease the risk of PD.[12,13] Until now, the risk of developing PD and the impact of systemic therapy on this risk in patients with psoriasis have not been thoroughly investigated. Therefore, the objectives of this study were to determine the incidence rate and the risk factors for the development of PD in patients with psoriasis by evaluating the data from National Health Insurance Service (NHIS) database.

CAPSULE SUMMARY

- The association between psoriasis and Parkinson disease remains unclear. This study showed that patients with psoriasis had an increased risk of Parkinson disease and that this risk was low among those on systemic therapy.
- Systemic anti-inflammatory agents for psoriasis could prevent the development of Parkinson disease in psoriasis patients.

MATERIALS AND METHODS

Data source

The Korean NHIS database is managed by the Korean government and covers almost 100% of the Korean population (~51 million people).[14] The Korean NHIS is a computerized database that provides health care–related data on all types of claims (including those for prescriptions and procedures), outpatient and inpatient care records, diagnoses by ICD-10 (International Classification of Disease, 10th Revision) codes, as well as the age and sex of patients.[15] In the Korean NHIS, all identifiable information of patients is reidentified and given a unique number. This study was approved by the institutional review board of the Korean National Institute for Bioethics Policy (approval no. NHIS-2018-1-224) and the institutional review board of the Catholic University of Korea (approval no. KC18ZESI0387).

Study population

All included patients were ≥20 years of age, had visited clinics or hospitals >1 time during the study period (January 2007-December 2014), and had the ICD-10 diagnostic code for psoriasis (L40). We analyzed individuals with psoriasis (N = 548,327) and control patients without psoriasis (N = 2,741,635) who were randomly selected and age- and sex-matched at a 5-to-1 ratio with the study patients during the same period. The psoriasis group was further classified into a systemic therapy–exposed psoriasis group and a systemic therapy–unexposed psoriasis group. The systemic therapy–exposed psoriasis group included psoriasis patients who had been prescribed ≥1 systemic agent (ie, acitretin, cyclosporine, methotrexate, a biologic [eg, adalimumab, etanercept, infliximab, ustekinumab]) more than once. The primary endpoint was newly diagnosed PD, which was identified by the registration of the ICD-10 code (G20) with the Reliable Rare Incurable Disease System in the Korean NHIS database.[16] Patients with PD diagnoses before study enrollment were excluded. The study was initiated after a 1-year washout period (during 2005-2006) to reduce the confounding effect of previously diagnosed PD on the study outcomes.

Statistical analysis

Baseline demographic characteristics were presented as mean ± standard deviation or number (%). Control patients, systemic therapy–unexposed patients with psoriasis, and systemic therapy–exposed patients with psoriasis were compared by using analysis of variance (Table I). The incidence rate of PD was calculated by dividing the total number of incident cases of PD by the entire follow-up duration (person-years). The incidence probability of PD according to the presence or absence of psoriasis and systemic therapy for psoriasis was calculated by using Kaplan-Meier curves. The log-rank test was used to analyze the differences between the study and control groups. Hazard ratios (HRs) and 95% confidence interval (CI) values for the incidence of PD in psoriasis were determined by using a Cox proportional hazard model after stratifying by age, sex, and covariates. Multivariate Cox regression models were used to assess the risk of PD after

Abbreviations used:

CI: confidence interval
HR: hazard ratio
ICD-10: International Classification of Diseases, 10th Revision
IL: interleukin
NHIS: National Health Insurance Service
PD: Parkinson disease
RXR: retinoid X receptor
T_H1: T-cell helper 1
T_H17: T-cell helper 17
TNF-α: tumor necrosis factor α

adjusting for confounding factors, including age, sex, income level, diabetes mellitus, hypertension, and dyslipidemia. *P* values <.05 were considered statistically significant. The data were analyzed by using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the study population

In the psoriasis group, 511,494 patients had not received systemic drugs for psoriasis (systemic therapy−unexposed psoriasis group), and 36,833 patients received systemic treatment for psoriasis (systemic therapy−exposed psoriasis group). The baseline demographics are shown in Table I.

The incidence and risk of PD among psoriasis patients

The incidence rate of PD was 0.673 cases/1000 person-years in the control group and 0.768 cases/1000 person-years in the psoriasis group (systemic therapy−unexposed incidence 0.782 cases/1000 person-years; systemic therapy−exposed incidence 0.560 cases/1000 person-years). After adjusting for age, sex, income level, diabetes, hypertension, and dyslipidemia, the psoriasis group showed a significantly increased risk of developing PD (HR 1.091, 95% CI 1.029-1.115) compared with the control group. The psoriasis group was further analyzed for the effect of systemic therapy. The risk of PD was significantly higher among the psoriasis patients who were not receiving systemic therapy (HR 1.093, 95% CI 1.031-1.159) and was low among the patients with psoriasis on systemic therapy (HR 1.04, 95% CI 0.806-1.316; Table II). The Kaplan-Meier plot analysis showed that the risk of PD increases with duration of disease (Fig 1, *A*). Furthermore, the risk was higher in the systemic therapy−unexposed psoriasis group than in the systemic therapy−exposed psoriasis group (Fig 1, *B*).

In addition, we investigated the preventive effect of specific systemic therapies on PD (Table III). Acitretin, methotrexate, and cyclosporine decreased the risk of PD; however, anti-tumor necrosis factor α (TNF-α) biologics (etanercept, infliximab, and adalimumab) did not decrease the risk of PD (Table III). Moreover, in the subgroup analysis of patients who had taken systemic therapy for >1 year, the risk of PD was more significantly reduced (Table IV). Similarly, acitretin, methotrexate, and cyclosporine decreased the risk of PD and anti-TNF-α biologics did not (Table IV).

DISCUSSION

The results of this study revealed a significantly increased risk of PD in patients with psoriasis. Our study also demonstrated an increased overall risk of PD in psoriasis patients after adjusting for the confounding factors. Interestingly, we observed that patients with psoriasis who received systemic therapy had a lower risk of PD than those who were not exposed to systemic therapy.

Rugbjerg et al reported no increased risk of PD with psoriasis in 13,695 Danish patients with psoriasis (odds ratio 0.96, 95% CI 0.85-1.08).[17] In a study conducted in Sweden, the risk of PD in

Table I. Comparison of the demographics of the control and psoriasis groups

Characteristic	Control	Psoriasis group		*P* value
		Systemic therapy−unexposed	Systemic therapy−exposed	
N	2,741,635	511,494	36,833	
Sex, male, n (%)	1,461,865 (53.32)	271,276 (53.04)	21,097 (57.28)	<.0001
Mean age ± SD, y	57.97 ± 11.99	58.15 ± 12.05	55.56 ± 10.78	<.0001
Age ≥40 y and <64 y, n (%)	1,921,690 (70.09)	355,339 (69.47)	28,999 (78.73)	<.0001
Diabetes mellitus, n (%)	293,832 (10.72)	70,900 (13.86)	4858 (13.19)	<.0001
Hypertension, n (%)	771,828 (28.15)	167,766 (32.80)	10,225 (27.76)	<.0001
Dyslipidemia, n (%)	427,449 (15.59)	102,914 (20.12)	6935 (18.83)	<.0001
Mean ± SD follow-up duration, y	3.39 ± 2.02	3.41 ± 2.01	3.15 ± 2.03	<.0001

SD, Standard deviation.

Table II. The incidence rates and risk of incidence of Parkinson disease by study group

Group	Event	Duration	Incidence rate	Model 1*	Model 2†	Model 3‡
Control	6261	9,297,825.83	0.673	1 (Referent)	1 (Referent)	1 (Referent)
Psoriasis	1428	1,859,117.45	0.768	1.141 (1.077-1.208)	1.141 (1.077-1.208)	1.091 (1.029-1.155)
Systemic therapy—unexposed	1363	1,743,008.81	0.782	1.161 (1.095-1.231)	1.144 (1.078-1.212)	1.093 (1.031-1.159)
Systemic therapy—exposed	65	116,108.64	0.560	0.833 (0.646-1.054)	1.086 (0.842-1.374)	1.04 (0.806-1.316)

*Model 1: nonadjusted.
†Model 2: adjusted by age and sex.
‡Model 3: adjusted by age, sex, income level, diabetes mellitus, hypertension, and dyslipidemia.

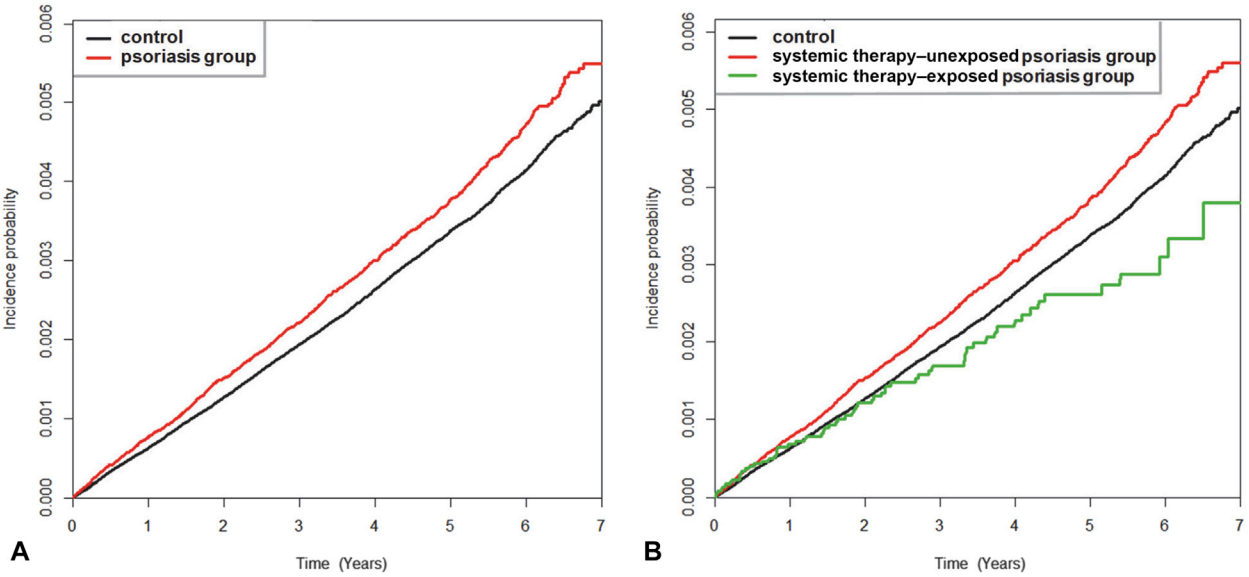

Fig 1. Kaplan-Meier curves showing incidence of Parkinson disease (PD) in psoriasis patients and controls. **A**, Incidence of PD is significantly higher in psoriasis patients than control individuals. **B**, Psoriasis patients who received systemic therapy had a lower incidence of PD than psoriasis patients not given systemic therapy. *PD*, Parkinson disease.

psoriasis patients was found to be not significant (HR 1.25, 95% CI 0.95-1.65).[4] Sheu et al observed a significant difference (HR 1.74, 95% CI 1.35-2.20) in the risk of PD in psoriasis patients compared with the control group.[10] A recent meta-analysis showed that the pooled risk of PD in patients with psoriasis was significant (1.38%, 95% CI 1.15%-1.66%).[11] Our study also found that the risk of developing PD (HR 1.091, 95% CI 1.029-1.115) was significantly increased in psoriasis patients compared with controls, although the HR is relatively marginal.

Psoriasis is related to numerous comorbidities, including cardiovascular diseases, arthritis, malignancies, and metabolic diseases.[18,19] The pathogenesis of psoriasis remains unclear; however, immune-mediated inflammation and genetic factors are considered as etiologic factors.

Neuroinflammation and immune responses play an important role in the development and progression of PD, which is characterized by progressive degeneration of the dopaminergic neurons.[20] In addition, α-synuclein (Lewy body) aggregation, oxygen free radicals, and death of the nigrostriatal dopaminergic neurons have been implicated in the development of PD.[20] Neuroinflammation mediated by microglia, a major immune cell in the brain, induces the degeneration of the dopaminergic neurons.[21,22] Inflammation caused by activated glial cells can induce oxidative damage to the nigrostriatal pathway. Increased nitration of α-synuclein and activation of Toll-like receptors contribute to neuroinflammation through their activation of proinflammatory cytokines and chemokines.[23] During adaptive immunity, chronic inflammation, T-cell infiltration, and glial cell activation play pivotal roles in the degeneration of the dopaminergic neurons.[24] Interestingly, T-cell helper 1 (T_H1) or T-cell helper 17 (T_H17) cells from nitrated

Table III. The risk of Parkinson disease in psoriasis patients by exposure to specific systemic therapies

Group	n	Event	Duration	Incidence rate	Model 1*	Model 2†	Model 3‡
Psoriasis							
Systemic therapy—unexposed	511,494	1363	1,743,008.81	0.782	1 (Referent)	1 (Referent)	1 (Referent)
Systemic therapy—exposed	36,833	65	116,108.64	0.560	0.717 (0.559-0.92)	0.939 (0.732-1.206)	0.939 (0.732-1.206)
Acitretin	21,610	40	97,514.34	0.4102	0.674 (0.492-0.922)	0.882 (0.644-1.208)	0.887 (0.647-1.215)
Methotrexate	4286	8	18,669.06	0.42852	0.712 (0.355-1.426)	0.942 (0.47-1.888)	0.953 (0.475-1.909)
Cyclosporine	13,992	16	48,969.62	0.32673	0.59 (0.36-0.965)	0.793 (0.484-1.299)	0.777 (0.474-1.273)
Anti-TNF-α§	65	2	256.34	7.80223	13.512 (3.376-54.08)	22.386 (5.605-89.403)	21.773 (5.451-86.962)

TNF-α, Tumor necrosis factor α.
*Model 1: nonadjusted.
†Model 2: adjusted by age and sex.
‡Model 3: adjusted by age, sex, income level, diabetes mellitus, hypertension, and dyslipidemia.
§Anti-TNF-α treatments, including etanercept, infliximab and adalimumab.

α-synuclein—immunized donor mice exhibit severe dopaminergic neuronal death in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine—intoxicated mice, which is a PD mouse model.[25]

There is increasing evidence that PD and psoriasis have overlapping mechanisms of pathogenesis. First, as mentioned before, the probable pathomechanisms for both diseases include chronic inflammatory reactions. Several studies have demonstrated an increased risk of neurodegenerative disorder or dementia in patients with chronic autoimmune inflammatory disorders.[26-28] Proinflammatory cytokines, such as TNF-α, interleukin (IL) 1, and IL-6, are elevated in both psoriasis and PD.[5,29] In addition, the dysregulation of IL-10 could lead to the development of both diseases.[30,31] Increased levels of cytokines, including TNF-α, IL-1β, IL-6, IL-12, and interferon γ, are found in the brains and cerebrospinal fluid of patients with PD, and activated microglial cells are observed in the brains of these patients.[32,33] In chronic inflammatory environments, microglial activation can result in the liberation of free radicals, reactive oxygen or nitrogen species, prostaglandins, or cytokines, which can lead to neuronal damage.[10,34,35]

Second, as previously mentioned, the immune response could have an essential role in the development of both diseases. In psoriasis, IL-23 induces the differentiation of naive T cells into T_H17 cells, and IL-12 promotes differentiation of naive T cells into T_H1 cells.[5] Interestingly, in patients with PD, a significant increase in the number of T_H17 and myeloid-derived suppressor cells are observed in peripheral blood.[36] In addition, a positive correlation is observed between these cells.[37]

Witoelar et al identified potentially shared genetic risk factors, such as *SETD1A* and *BC070367*, in patients with PD and psoriasis.[38] According to the study by Dzamko et al, the genetic variations associated with inflammation also stressed the role of inflammation in the pathomechanism of PD.[39]

We observed that patients with psoriasis who were treated with current systemic therapies had a lower risk of PD than those who were not treated with systemic therapy. Acitretin is a widely used retinoid for the systemic treatment of psoriasis and is a ligand of the retinoid acid receptors and retinoid X receptor (RXR).[40] Previous reports confirmed the presence of endogenous RXR ligands in the embryonic central nervous system. RXR ligands have been implicated in the survival of the dopaminergic neurons and proposed as targets for PD therapeutics.[41] In clinical studies, patients with a history of regular or chronic intake of nonsteroidal anti-inflammatory drugs had shown a decreased risk

Table IV. The risk of Parkinson diseases in psoriasis patients by exposure to specific systemic therapies for >1 year

Group	n	No. events	Duration	Incidence	Model 1*	Model 2†	Model 3‡
Psoriasis							
Systemic therapy—unexposed	511,494	1363	1,743,008.81	0.782	1 (Referent)	1 (Referent)	1 (Referent)
Systemic therapy—exposed ≥1 y	14,258	22	44,220.31	0.49751	0.637 (0.418-0.971)	0.853 (0.559-1.3)	0.853 (0.559-1.3)
Acitretin	8226	16	28,422.35	0.56294	0.72 (0.44-1.178)	0.972 (0.593-1.591)	0.979 (0.598-1.603)
Methotrexate	1886	1	5957.06	0.16787	0.215 (0.03-1.526)	0.304 (0.043-2.14)	0.309 (0.044-2.175)
Cyclosporine	5370	5	13,320.19	0.37537	0.485 (0.201-1.166)	0.647 (0.269-1.556)	0.632 (0.263-1.522)
Anti-TNF-α§	33	1	87.85	11.3828	14.722 (2.072-104.588)	27.151 (3.82-192.98)	24.795 (3.487-176.286)

TNF-α, Tumor necrosis factor α.
*Model 1: nonadjusted.
†Model 2: adjusted by age and sex.
‡Model 3: adjusted by age, sex, income level, diabetes mellitus, hypertension, and dyslipidemia.
§Anti-TNF-α treatments, including etanercept, infliximab and adalimumab.

of PD.[12,42] In particular, ibuprofen was associated with a lower risk of developing PD.[1,43] These reports could be indirect evidence supporting the role of chronic inflammation in the pathogenesis of PD and might explain the lower risk of PD in patients with psoriasis who had received systemic treatment. In a Danish study, the systemic anti-inflammatory therapies, such as biologics and methotrexate, decreased the risk of cardiovascular disease in patients with severe psoriasis compared with other antipsoriatic treatments.[6] Therefore, we assume that systemic anti-inflammatory agents against psoriasis can be potentially neuroprotective by modulating the inflammatory response of the whole body and could reduce the incidence of PD in patients with psoriasis. However, further analysis showed that acitretin, methotrexate, and cyclosporine decreased the risk of PD. By contrast, anti-TNF-α biologics (etanercept, infliximab, and adalimumab) did not decrease the risk of PD (Table IV). This result might have been caused by the small number (n = 65) of patients with psoriasis who had used anti-TNF-α biologics. In addition, we performed an additional subgroup analysis for patients who had undergone systemic therapy for >1 year (Table IV). The risk of PD was more significantly reduced in the group who had undergone systemic therapy for >1 year. Furthermore, acitretin, methotrexate, and cyclosporine decreased the risk of PD; however, anti-TNF-α biologics did not decrease PD risk because of the limited number of patients (n = 33) who used biologics. The use of biologics in Korea has been increasing recently, and we expect that analyses on biologics conducted in the near future will yield some interesting results.

The strengths of our study include the use of a large, population-based cohort, a population showing an association between PD and psoriasis. In addition, to the best of our knowledge, this study showed for the first time that systemic anti-inflammatory drugs could reduce the risk of PD in patients with psoriasis. However, there are several limitations. First, patients were included on the basis of registered diagnostic codes alone. Second, because our study was not prospective, accurately estimate the causal relationship was difficult. To avoid the possible effects of reverse causality, we established a 1-year washout period and excluded persons with pre-existing PD. Third, we did not have data regarding other factors that could affect the incidence of PD, such as smoking, drinking status, and family history of PD. To minimize this possibility, we used a multivariable Cox proportional hazards model to determine the HR for developing PD, after adjusting for the confounding variables.

Nonetheless, we could not adjust for all confounding variables, such as health care systems and environmental factors, which vary by geography; therefore, the results of this study might not be generalizable to other populations.

In conclusion, we observed a significant increase in the incidence of PD in patients with psoriasis compared with that of patients without psoriasis and a reduction in the risk of PD in patients receiving systemic treatment for psoriasis. These results suggest that inflammation plays an important role in the pathogenesis of both diseases, and reducing inflammation might protect against the development of PD in patients with psoriasis. Further research is required to explore the shared pathogenesis of PD and psoriasis.

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