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Reduced Risk of Parkinson Disease in Patients With Rheumatoid Arthritis: A Nationwide Population-Based Study

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Abstract

Objective: To investigate the association between rheumatoid arthritis (RA) and the risk of developing Parkinson disease (PD).

Patients and Methods: This retrospective cohort study was conducted from January 1, 1998, through December 31, 2010, using data from the Taiwan National Health Insurance Research Database. We identified 33,221 patients with newly diagnosed RA and 132,884 randomly selected age- and sex-matched patients without RA. A multivariable Cox proportional hazards regression model was used to evaluate the risk of developing PD in the RA cohort.

Results: The multivariable Cox proportional hazards regression analysis revealed an adjusted hazard ratio of 0.65 (95% CI, 0.58-0.73) for the development of PD in the RA cohort relative to the non-RA cohort. The cumulative incidence of PD was 2.42% lower in the RA cohort than in the non-RA cohort. The risk reduction of PD development in patients affected with RA was independent of treatment with disease-modifying antirheumatic drugs (DMARDs); subgroup analysis of patients treated with biologic DMARDs revealed further risk reduction (adjusted hazard ratio, 0.57; 95% CI, 0.41-0.79).

Conclusion: Patients with RA have a reduced risk of developing PD. This risk reduction was independent of treatment with DMARDs; however, biologic DMARDs appear to further reduce this risk. Further research is necessary to explore the underlying mechanism.

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder typically affecting women and elderly people.[1] Rheumatoid arthritis primarily damages the joints; however, it can cause extra-articular abnormality, such as lesions in the central nervous system (CNS).[2] Studies[3-5] have reported increased risks of depression, stroke, and dementia in patients with RA; the mechanism underlying CNS involvement is unclear, but chronic inflammatory processes are considered a key factor.

Parkinson disease (PD), the second most common neurodegenerative disease, is a progressive long-lasting disease characterized by the combination of resting tremor, rigidity, bradykinesia, and postural instability. The main pathological hallmark of PD is the progressive and selective degeneration of dopaminergic neurons in the substantia nigra pars compacta. Although the etiology of PD is largely unknown,[6] growing evidence suggests that neuroinflammation contributes to PD.[7,8] The activation of microglia and increase of pro-inflammatory factors have been associated with the degeneration of dopaminergic neurons in patients with PD and in PD animal models.[9]

The association between RA and the risk of developing PD is unclear. Although some cases of RA and coexisting PD have been reported,[10] the association between RA and PD remains elusive. In addition, epidemiological studies[11,12] have suggested that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with a reduced risk of developing PD. However, the effect of disease-modifying antirheumatic drugs (DMARDs), a common treatment for slowing or preventing joint destruction in RA, on PD

is unknown. To address these uncertainties, we designed this nationwide population-based study to investigate the possible association between RA and the risk of developing PD. We hypothesize that chronic inflammatory mediators involved in RA might be crucial in the pathogenesis of PD and that DMARDs might have a moderating effect on PD development.

PATIENTS AND METHODS

Data Source

Taiwan's Bureau of the National Health Insurance launched the National Health Insurance Program in 1995, a program currently covering approximately 99% of the 23.74 million residents of Taiwan.[13] The National Health Research Institutes was commissioned to construct and maintain the National Health Insurance Research Database (NHIRD) for research. The NHIRD includes comprehensive data on the inpatient care, ambulatory care, dental care, and prescription drugs availed by the insurants as well as their sex and date of birth. Pursuant to the Personal Information Protection Act, insurants' identification codes are scrambled before release for research. The diagnoses recorded in the NHIRD are coded according to the *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*). This study was approved by the Ethics Review Board of China Medical University (CMUHIO4-REC2-115).

Case Definition and Cohort Formation

We used the Registry for Catastrophic Illness Patient Database (RCIPD), a subset of the NHIRD, to identify patients with RA (*ICD-9-CM* 714). In Taiwan, rheumatologists can apply for a catastrophic illness card on behalf of any patient with RA who satisfies at least 4 of the 1987 American College of Rheumatology criteria, and patients with these cards are exempt from co-payment. These applications are scrutinized through peer reviews. From the RCIPD, we identified 33,221 patients with newly diagnosed RA between January 1, 1998, and December 31, 2010. The date of RA diagnosis was defined as the index date. For each patient with RA, 4 RA-free controls were frequency-matched for age (5-year intervals), sex, and year of RA diagnosis. In both RA and non-RA cohorts, patients with previous PD (*ICD-9-CM* 332) and those with incomplete information were excluded.

Outcome

Each patient was followed from the index date to the date of PD diagnosis, withdrawal from the insurance program, censoring because of death, or December 31, 2011.

Comorbidities and Medication

We considered potential risk factors, namely, diabetes (*ICD-9-CM* 250), hypertension (*ICD-9-CM* 401-405), hyperlipidemia (*ICD-9-CM* 272), coronary artery disease (CAD) (*ICD-9-CM* 410-414), head injury (*ICD-9-CM* 310.2, 800, 801, 803, 804, 850, 851, 853, and 854), depression (*ICD-9-CM* 296.2, 296.3, 296.82, 300.4, and 311), and stroke (*ICD-9-CM* 430-438). All risk factors were defined before the index date. In addition, medications for RA, namely, NSAIDs and

TABLE 1. Characteristics of Patients With Rheumatoid Arthritis and Those Without Rheumatoid Arthritis[a]

Characteristic	Rheumatoid arthritis: Yes (n=33,221) n	%	Rheumatoid arthritis: No (n=132,884) n	%	*P* value
Age (y)					.99
20-34	3,129	9.4	12,516	9.4	
35-49	9,925	29.9	39,700	29.9	
50-64	12,586	37.9	50,344	37.9	
≥65	7,581	22.8	30,324	22.8	
Mean±SD[b]	53.9±13.9		53.4±14.3		<.001
Sex					.99
Female	25,782	77.6	103,128	77.6	
Male	7,439	22.4	29,756	22.4	
Comorbidity					
Diabetes	2,860	8.6	11,373	8.6	.77
Hypertension	10,806	32.5	41,100	30.9	<.001
Hyperlipidemia	6,668	20.1	26,507	20.0	.61
Coronary artery disease	5,361	16.1	19,450	14.6	<.001
Head injury	4,695	3.5	1,267	3.8	.01
Depression	2,435	7.3	6,824	5.1	<.001
Stroke	883	2.7	3,984	3.0	<.001
Medications					
NSAIDs	16,103	48.5	57,370	43.2	<.001
DMARDs	16,941	51.0			
Biologic DMARDs	5,037	15.2			

[a]DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug.
[b]*t* test; others: χ^2 test.