Risk of Parkinson disease in Sjögren syndrome administered ineffective immunosuppressant therapies
A nationwide population-based study

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Abstract
To determine the incidence and risk of Parkinson disease (PD) in patients with Sjögren syndrome (SS) according to a nationwide population-based database.

In total, 12,640 patients in the SS cohort and 50,560 in the non-SS cohort were enrolled from Taiwan’s National Health Insurance Research Database from 2000 to 2010. We used the Cox multivariable proportional hazards model to determine the risk factors for PD in the SS cohort.

We observed an increased incidence of PD in patients with SS, with a crude hazard ratio (HR) of 1.40 and an adjusted HR (aHR) of 1.23. The cumulative incidence of PD was 1.95% higher in the SS cohort than in the non-SS cohort. The SS cohort had an elevated HR under medication use, namely cevimeline and pilocarpine (crude HR, 1.28), hydroxychloroquine (crude HR, 1.43; aHR, 1.46), and methylprednisolone (crude HR, 2.21; aHR, 1.49). Patients receiving other non-hydroxychloroquine immunosuppressant therapies had a lower risk (aHR, 0.86) of PD. Furthermore, patients with SS aged 20 to 49 years had a 1.93-fold higher risk of PD than did those without SS (aHR, 1.93). The risk of PD was higher (aHR, 2.20) in patients with SS without comorbidities than in those with comorbidities. The aHR of PD significantly increased when the follow-up period exceeded 9 years (aHR, 1.93).

We determined an increased risk of PD in patients with SS. Further investigation is warranted to determine the possible underlying mechanisms and the potential role of non-hydroxychloroquine immunosuppressants in ameliorating PD.

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, ICD-9-CM = International Codes of Disease Ninth Edition Clinical Modification, LHID2000 = Longitudinal Health Insurance Database, NHII = National Health Insurance, NHIRD = National Health Insurance Research Database, PD = Parkinson disease, SS = Sjogren syndrome

Keywords: longitudinal health insurance database, national health insurance research database, Parkinson disease, Sjögren syndrome

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1. Introduction

Sjögren syndrome (SS) is a systemic chronic inflammatory and autoimmune disorder characterized by lymphocytic infiltrates in exocrine organs, typically the lacrimal and salivary glands, causing dryness of the eyes and mouth. A recent study confirmed that primary SS has a systemic expression, including glanulard and extraglandular manifestations such as neurological involvement.[1-4] For diseases that affect both the peripheral and central nervous systems, various neurological manifestations may occur in those with SS.[5-7] Parkinson disease (PD) is a progressive neurodegenerative disease with the cardinal symptoms of tremor, bradykinesia, rigidity, and postural instability.[8] The pathophysiology of PD is dopamine-cell death in the pars compacta region of the substantia nigra[9] that results in major disruptions in the connections to the thalamus and motor cortex.

Some immune system-mediated mechanisms have been proposed to illustrate the possible pathogenic mechanisms through which autoantibodies cause dopaminergic cell death.[10,11] Benkler et al[12] reported that inflammatory autoantibodies, namely antineuronal-cells, anti-brain lysate, anti-dsDNA, may contribute to the clinical manifestations of PD. The ICAM4, Myotilin, Fibronectin 1 and Pentatricopeptide repeat domain 2 can also be detected in PD sera.[13] Sera from patient with SS who have autonomic neuropathy is also related to circulating anti-ganglionic acetylcholine receptor antibodies.[14]

We designed this study to assess the risk of PD in patients with SS and to recognize the associated risk factors. We also evaluated the association between SS and the risk of PD and observed a higher risk of PD in patients with SS.

2. Methods

2.1. Data source

The National Health Insurance (NHI) program was established on March 1, 1995 to provide comprehensive medical care to the 23.54 million residents of Taiwan.[15] The NHI Research Database (NHIRD), maintained by the National Health Research Institutes (NHRI), contains claims records from the universal NHI program. The NHIRD has been described in detail in previous studies.[16,17] The NHRI encrypts the original electronic medical information to protect patient privacy before releasing the NHIRD for research purposes. In this study, we used a subset of the NHIRD containing health care data, namely the Longitudinal Health Insurance Database for Catastrophic Illness Patients (LHID-CIP), and the Registry of Beneficiaries. The diagnoses and procedures recorded in the NHIRD are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Ethics Review Board of China Medical University and Hospital in Taiwan approved this study (CMUH-104-REC2–115-CR3).

2.2. Patients

Patients newly diagnosed with SS (ICD-9-CM code 710.2) from 2000 to 2010 were identified from the LHID-CIP. The SS was diagnosed on the basis of ICD-9-CM codes, which were judged and determined by related specialists and physicians according to the standard clinical and laboratory criteria (ocular symptoms, oral symptoms, ocular signs, histopathology, salivary gland involvement, and autoantibodies, which met 4 of the 6 revised international classification criteria that were established by the American–European Consensus Group for diagnosing SS and 3 of the 4 objective criteria). The date of SS diagnosis was defined as the index date. Patients with a history of PD (ICD-9-CM 332) and aged <20 years were excluded. For the non-SS cohort, we randomly selected patients without a history of SS from the LHID-CIP, with exclusion criteria similar to those used for the SS cohort. Each patient with SS was frequency-matched with 4 patients without SS according to age (at 5-y intervals), sex, and the year of the index date.

2.3. Outcomes, comorbidities, and medications

The follow-up period began on the index date and continued until PD diagnosis; withdrawal from the NHI program; or December 31, 2011. Preexisting comorbidities included hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (ICD-9-CM codes 410–414), head injury (ICD-9-CM codes 310.2, 800, 801, 803, 804, 830, 851, 853, and 854), depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, and 311), and stroke (ICD-9-CM codes 430–438). In addition, the use of non-steroidal anti-inflammatory drugs (NSAIDs), statins, angiotensin-converting enzyme inhibitors, and beta-blockers was also collected.

2.4. Statistical analysis

We used the Chi-square test to compare the distributions of categorical variables and baseline comorbidities between the SS and non-SS cohorts. Differences in continuous variables between the cohorts were examined through the Student t test. The cumulative incidence of PD in the SS and non-SS cohorts was assessed through the Kaplan–Meier method; the log-rank test was used to compare the 2 cohorts. The incidence densities (per 1000 person-y) of PD were calculated for both cohorts.

Univariable and multivariable Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of PD development in the SS cohort compared with the non-SS cohort, with stratification based on sex, age, comorbidities, and the follow-up period. The multivariable Cox models were simultaneously adjusted for age, sex, and the comorbidities of hypertension, diabetes, hyperlipidemia, coronary artery disease, head injury, depression, and stroke. Furthermore, we evaluated the effects of biological therapies and anti-SS drugs on the risk of PD in the SS cohort. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC), with the significance level set to 0.05 in 2-tailed tests.

3. Results

The SS and non-SS cohorts included 12,640 and 50,560 participants, respectively, with similar distributions of age and sex (Table 1). The majority of the participants were aged ≤49 years (39.4%; mean age, approximately 54 y), and 89.1% were women. Comorbidities of hyperlipidemia, coronary artery disease, head injury, and depression were more prevalent in the SS cohort than in the non-SS cohort (P < .05), but diabetes was more prevalent in the non-SS cohort. The mean follow-up period for PD in the SS and non-SS cohorts was 5.21 (standard deviation [SD], 3.15) and 5.18 (SD, 3.16) years, respectively. The Kaplan–Meier survival graph indicated that the cumulative incidence of PD was 1.95% higher in the SS cohort than in the
The most common medications used for SS were cevimeline and pilocarpine (36.5%), hydroxychloroquine (27.1%) and non-hydroxychloroquine immunosuppressant therapies (17.5%).

The overall incidence of PD was 1.40-fold higher in the SS cohort than in the non-SS cohort (2.42 vs 1.73 per 1000 person-y; 95% CI, 1.32–1.48). After adjustment for age, sex, and comorbidities, participants with SS had a higher risk of PD than did those without SS (adjusted HR [aHR], 1.23; 95% CI, 1.16–1.30; Table 2). The sex-specific risk of PD was significantly higher in women (aHR, 1.28; 95% CI, 1.21–1.36), and the incidence of PD decrease with age. The risk of PD was 1.93- and 1.14-fold higher in participants aged 20 to 49 (aHR, 1.93; 95% CI, 1.75–2.13) and 50 to 64 (aHR=1.41; 95% CI=1.28–1.55) years, respectively, than in those without SS. Furthermore, the risk of PD was significantly higher in participants with SS than in those without SS after stratification without any comorbidities (aHR, 2.20; 95% CI, 2.04–2.38) and with at least one comorbidity (aHR, 1.20; 95% CI, 1.11–1.30). The aHR of PD significantly increased with the follow-up period of more than 9 years (aHR, 1.93; 95% CI, 1.66–2.23). The SS cohort had a higher risk of PD than did the non-SS cohort throughout the follow-up period.

Compared with the participants without SS, the participants with SS to whom hydroxychloroquine was administered had a significantly higher risk of PD (aHR, 1.46; 95% CI, 1.34–1.59). Moreover, the risk of PD was higher in participants with SS to whom cevimeline and pilocarpine (aHR, 1.30; 95% CI, 1.23–1.39), hydroxychloroquine (aHR, 1.14; 95% CI, 1.07–1.21), and methylprednisolone (aHR, 1.22; 95% CI, 1.16–1.29) were not administered. Participants under other non-hydroxychloroquine immunosuppressant therapies had a relatively lower risk of PD (aHR, 0.86; 95% CI, 0.73–1.01; Table 3).

### 4. Discussion

As per our review of relevant literature, no large-scale cohort study has investigated the association between SS and PD. This study was the 1st extensive analysis of a nationwide population database of participants with SS and PD. Our findings revealed that SS increased the risk of PD. The aHR of PD significantly increased for the participants aged 20 to 49 years and gradually decreased for those aged >49 years. The crude HR of 1.40 (95% CI, 1.38–1.48), with an aHR of 1.23 (95% CI, 1.16–1.30), for

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**Table 1**

| Characteristics of patients with and without Sjögren syndrome. | Sjögren syndrome (N=12640) | No (N=50560) | P-value |
|---|---|---|---|
| Age, y | n | % | n | % |
| 20–49 | 4984 | 39.4 | 19936 | 39.4 | .99 |
| 50–64 | 4820 | 38.1 | 19280 | 38.1 |
| ≥65 | 2836 | 22.4 | 11344 | 22.4 | .006 |
| Mean (SD) | 53.4 | 14.2 | 53.8 | 13.9 | .99 |
| Sex | | | |
| Female | 11259 | 89.1 | 45036 | 89.1 |
| Male | 1381 | 10.9 | 5524 | 10.9 |
| Comorbidity | | | |
| Diabetes | 1050 | 8.31 | 4701 | 9.30 | .001 |
| Hypertension | 4089 | 32.4 | 16225 | 32.1 | .58 |
| Hyperlipidemia | 3276 | 25.9 | 11140 | 22.0 | <.001 |
| Coronary artery disease | 2712 | 21.5 | 7737 | 15.3 | <.001 |
| Head injury | 597 | 4.72 | 2141 | 4.23 | .02 |
| Depression | 1786 | 14.1 | 2732 | 5.40 | <.001 |
| Stroke | 465 | 3.20 | 1608 | 3.17 | .85 |
| Medication | | | |
| Immunosuppressant therapies | 2215 | 17.5 |
| Cholinergic agents: cevimeline, pilocarpine | 4609 | 36.5 |
| Biologic therapy: rituximab with prednisolone | 2491 | 19.7 |
| Methylprednisolone injection | 102 | 0.81 |
| Hydroxychloroquine | 3425 | 27.1 |

Chi-square test.

T test.
PD development was higher in the participants with SS. The participants with SS also had a higher risk of PD during the long-term follow-up period, and the participants without comorbidities had a notably elevated HR for PD (aHR, 2.20). The treatment of dry mouth caused by salivary gland hypofunction aims to alleviate symptoms. Participants with SS who received cevimeline and pilocarpine, which act as sialagogues agents, did not increase the HR for PD in our study (aHR, 1.30). However, there was an increasing of the HR for those who received methylprednisolone injection (aHR, 2.20). Patients with SS who did not receive methylprednisolone treatment had a higher risk (aHR, 1.22). Using other immunosuppressant therapies (azathioprine, cyclosporine, mycophenolate, and tacrolimus) yielded a relatively lower risk of PD (aHR, 0.86) than did use other treatments.

Dopamine depletion from the basal ganglia results in major disruptions in the connections to the thalamus and motor cortex, facilitating the development of PD. Previous studies have proposed that inflammation plays a crucial role in the pathogenesis of PD and its neurodegeneration probably involves either programmed cell death (apoptosis) or necrosis. Patients with SS have been hypothesized to have an increased risk of PD, and the etiology of PD may be associated with inflammatory autoantibodies, cardiovascular diseases, and Alzheimer disease.

| Table 2 | Incidence and hazard ratio of Parkinson disease in patients with and without Sjögren syndrome. |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
| Outcome | Yes | No | Crude HR | Adjusted HR |
| Event | PY | Rate | Event | PY | Rate | 95% CI | 95% CI |
| All | 159 | 65805 | 2.42 | 452 | 261929 | 1.73 | 1.40 (1.32, 1.48) | 1.23 (1.16, 1.30) |
| Sex | | | | | | | | |
| Female | 131 | 58744 | 2.23 | 354 | 233655 | 1.52 | 1.47 (1.38, 1.57) | 1.28 (1.21, 1.36) |
| Male | 28 | 7061 | 3.97 | 98 | 28274 | 3.47 | 1.14 (0.96, 1.36) | 1.00 (0.85, 1.18) |
| Age, y | | | | | | | | |
| 20–49 | 15 | 28252 | 0.53 | 21 | 111410 | 0.19 | 2.92 (2.56, 3.10) | 1.93 (1.75, 2.13) |
| 50–64 | 47 | 24578 | 1.91 | 111 | 98268 | 1.13 | 1.69 (1.54, 1.86) | 1.41 (1.28, 1.55) |
| ≥ 65 | 97 | 12975 | 7.46 | 320 | 52250 | 6.12 | 1.22 (1.09, 1.37) | 1.11 (0.88, 1.24) |
| Comorbidity | | | | | | | | |
| No | 31 | 31286 | 0.99 | 76 | 149049 | 0.51 | 1.94 (1.79, 2.11) | 2.20 (2.04, 2.38) |
| Yes | 128 | 34519 | 3.71 | 376 | 112880 | 3.33 | 1.11 (1.03, 1.21) | 1.20 (1.11, 1.30) |
| Follow time, years | | | | | | | | |
| ≤ 3 | 82 | 33382 | 2.46 | 222 | 132921 | 1.67 | 1.47 (1.38, 1.56) | 1.25 (1.18, 1.32) |
| 4–6 | 77 | 19704 | 3.91 | 230 | 78360 | 2.94 | 1.33 (1.24, 1.43) | 1.22 (1.14, 1.31) |
| 7–9 | 23 | 3971 | 5.79 | 75 | 16145 | 4.65 | 1.25 (1.10, 1.42) | 1.26 (1.12, 1.43) |
| ≥ 10 | 9 | 2564 | 3.05 | 20 | 11907 | 1.67 | 1.65 (1.57, 1.73) | 1.95 (1.86, 2.02) |

PY: person-year; Rate*: incidence rate per 1000 person-years.
Crude HR*: relative hazard ratio.
Adjusted HR: hazard ratio adjusted for age, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, depression, stroke.
Comorbidity*: Patients with any one of the comorbidities (including diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, depression, and stroke) were classified as the comorbidity group.

Table 3 | Incidence and adjusted hazard ratio of Parkinson disease stratified by medication in patients with Sjögren syndrome. |
|---------|--------------------------------------------------------------------------------|
| Medication exposed | N | Event | PY | Rate* | Crude HR | Adjusted HR |
| Without Sjögren Syndrome | 50560 | 452 | 261929 | 1.73 | 1 (Reference) | 1 (Reference) |
| Sjögren Syndrome | | | | | | |
| Without immunosuppressant therapies | 10425 | 445 | 53149 | 2.73 | 1.58 (1.49, 1.68) | 1.28 (1.21, 1.36) |
| With immunosuppressant therapies | 2215 | 14 | 12636 | 1.11 | 0.66 (0.54, 0.79) | 0.86 (0.73, 1.01) |
| Without cholineric agents: cevimeline, pilocarpine | 8031 | 113 | 44953 | 2.51 | 1.46 (1.36, 1.56) | 1.30 (1.23, 1.39) |
| With cholineric agents: cevimeline, pilocarpine | 4609 | 46 | 20852 | 2.21 | 1.28 (1.16, 1.41) | 1.07 (0.97, 1.17) |
| Without Hydroxychloroquine | 9215 | 106 | 44366 | 2.39 | 1.38 (1.29, 1.48) | 1.14 (1.07, 1.21) |
| With Hydroxychloroquine | 3425 | 53 | 21439 | 2.47 | 1.43 (1.31, 1.57) | 1.46 (1.34, 1.59) |
| Without methylprednisolone injection | 12538 | 157 | 65281 | 2.40 | 1.39 (1.31, 1.48) | 1.22 (1.16, 1.29) |
| With methylprednisolone injection | 102 | 2 | 524 | 3.82 | 2.21 (1.41, 3.46) | 1.49 (0.98, 2.25) |

PY: person-year; Rate*: incidence rate per 1000 person-years.
Crude HR*: relative hazard ratio.
Adjusted HR: hazard ratio adjusted for age, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, depression, and stroke.

<sup>∗</sup><sup>P < 0.05</sup>, †<sup>P < 0.01</sup>, ‡<sup>P < 0.001</sup>.
The SS is a chronic autoimmune disease that is characterized by the presence of certain autoantibodies, namely anti-Ro/SSA and anti-La/SSB,[26] which, according to some criteria, are required for SS diagnosis. Patients may also have high antimicrobial antibodies, rheumatoid factor, and anti-acetylcholine receptors.[27–29] At presentation, neither a cure for SS nor a specific treatment is known to permanently restore gland secretion. We have observed that the risk of PD was directly proportional to the follow-up period of participants with SS.

Another concern is whether immunosuppressive agents are beneficial in preventing PD in patients with autoimmune diseases. A nationwide population-based study that investigated systemic lupus erythematosus (SLE) and PD reported a contrasting association, concluding that the regular use of immunosuppressants could have potential benefit of preventing neurodegeneration and, thus, the development of PD.[30] Rugbjerg et al suggested that, for patients with rheumatoid arthritis (RA), administering immunosuppressant therapy reduced the risk of PD by 30%.[31] In our study, the participants with SS who received non-hydroxychloroquine immunosuppressant therapies had a relatively lower risk of PD, whereas those who used other treatments had a higher risk of PD. Recent studies also demonstrated that immunotherapies have benefit for neuropathies.[32–34] We reasonably supposed that non-hydroxychloroquine immunosuppressive agents play a key role in reducing the risk of PD. Nevertheless, participants with SS still had a significantly higher risk for a long follow-up period of more than 9 years (aHR, 1.93). Further research is required to determine the association between connective tissue diseases and PD and between non-hydroxychloroquine immunosuppressive agents and PD.

Our study had some limitations. First, the NHIRD does not include comprehensive information on clinical, laboratory, and imaging examinations as well as autoantibodies that can be used as diagnostic biomarkers (anti-Ro/SSA and anti-La/SSB). We could not obtain information on a family history of PD, smoking habits, alcohol consumption, occupation, and lifestyle, all of which may be risk factors for PD. Furthermore, we could not analyze the further possible pathogenesis of PD in the participants with SS. Uncertainty regarding whether outpatients with SS comply with instructions for medication use was the 2nd limitation. Third, this study was a retrospective cohort study; this type of study typically has low statistical quality because of possible biases associated with adjustments. Fourth, the participants in our study were predominantly Asian, and other ethnic populations were not well represented in our study. Fifth, we usually administer cholinergic agents for SS patients with symptoms of dry mouth and immunosuppressive agents for those who have extraglandular manifestation; however, data on the timing, dosage, and duration of antiinflammatory or immunosuppressive agents were insufficient. In our NHIRD program, we could not distinguish whether the SS was primary or secondary to another autoimmune disease.

5. Conclusion

In conclusion, our study was the 1st to determine an increased risk of PD in patients with SS and that non-hydroxychloroquine immunosuppressant therapy may reduce this risk. Further research is warranted to determine the possible underlying mechanisms and the potential role of non-hydroxychloroquine immunosuppressants in ameliorating PD.

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