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Ankylosing Spondylitis and the Subsequent Risk of Sleep Disorders: A Retrospective Population-based Cohort Study in Taiwan

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Abstract

The prevalence of sleep disorders in patients with ankylosing spondylitis (AS) appeared high; however, large scale, population-based studies have not yet been performed. We aimed to examine the subsequent risk of sleep disorders among AS patients in a nationwide database in Taiwan. We conducted a retrospective cohort study using data from the National Health Insurance (NHI) system of Taiwan. The case cohort included 1,785 patients newly diagnosed with AS between 2000 and 2010. The date of diagnosis was defined as the index date. Each patient was randomly matched with four people without AS, according to gender, age, and the index year. The occurrence of sleep disorders was followed up until the end of 2011. The overall incidence of sleep disorders was 1.60-fold greater in the AS cohort than in the non-AS cohort (28.4 versus 17.6 per 1000 person-years), with a multivariable Cox method measured adjusted hazard ratio (HR) of 1.47 [95% confidence interval (CI) = 1.29–1.68]. In addition, we found that the incident obstructive sleep apnea (OSA) increased in the AS cohort than the non-AS one, but this was not significant (adjusted HR = 1.37, 95% CI = 0.75–2.51). AS patients had a significantly higher risk of developing sleep disorders than the general population. The incidence of OSA in AS patients was also higher; however, it was not statistically significant. (J Intern Med Taiwan 2016; 27: 79-88)

Key Words: Sleep disorder, Obstructive sleep apnea (OSA), Ankylosing spondylitis (AS), Autoimmunity

Introduction

Ankylosing spondylitis (AS) is a chronic, progressive, and systemic inflammatory disease with articular and extra-articular features.[1] While in the early phase, the disease involves the sacroiliac joints, and it may also involve the axial skeleton in the advanced phase.[2] The mean prevalence per 10,000 was 16.7 in Asia and the number of cases in Asia were calculated to be 4.63–4.98 million.[3] The

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definitive etiology of AS remains unclear; however, it is known to involve the interaction of genetic and environmental factors. AS is associated with human leukocyte antigen-B27 (HLA-B27), which could modulate the inflammatory response via misfolding with an unfolded protein response and/or via antigen recognition. Therefore, some researchers consider that AS may be autoinflammatory rather than an autoimmune disease.[4]

Sleep disturbance plays an important role in patients with AS. Several studies have reported that sleep disorders in patients with AS are more common than in the general population. Jamieson et al.[5] reported sleep quality in AS (11 patients) differs from that in controls (11 controls). Hultgren et al.[6] reported that little sleep duration in 80.8% of the female and 50.0% of the male patients (total 60 patients) compared with 28.8% and 21.8%, respectively, in the reference group. Da Costa et al.[7] reported sleep problems are prevalent among patients with spondyloarthropathy (125 patients). Sleep complaints are associated with functional status, depressed mood, and stress. Hakkou et al.[8] reported sleep disturbance was found in 64.5% (71/110) among AS patients. Worse pain, high disease activity, and functional disability were present in AS patients with sleep disturbance. Similarly, sleep problems were significantly higher in AS patients with depression, anxiety, and poor quality of life. Batmaz et al.[9] reported AS patients (80 cases) had significantly more unfavorable scores in subjective sleep quality, habitual sleep efficiency domains, and the total Pittsburgh Sleep Quality Index (PSQI) score. In a recent study of the Chinese population, Li et al.[10] reported 58.6 (184/314) AS patients had a high risk for sleep disturbance. The PSQI score was also associated with age, education level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), overall health status, pain, morning stiffness, disease activity, depression, and anxiety.

However, most of the previous studies were performed either as a passive questionnaire or with small study populations. In addition, there are much fewer studies that have focused on the relationship between AS and obstructive sleep apnea (OSA).[11, 12] The present study attempts to determine the risk of sleep disorders in patients with AS by conducting a nationwide, population-based retrospective cohort study in Taiwan with data obtained from the National Health Insurance Research Database (NHIRD).

Materials and Methods

Data source

The Longitudinal Health Insurance Database 2000 (LHID 2000), released by the Taiwan National Health Research Institutes (NHRI) and Department of Health, provided the database for our study. The LHID 2000 contains all the original claim data of 1,000,000 beneficiaries, including inpatient care, ambulatory care, dental care, prescription drugs, and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes. The beneficiaries were randomly sampled from 23.74 million people in the Registry for Beneficiaries 2000, a system that covers almost 99% of the total population of Taiwan and contracted with 97% of clinics and hospitals. These data files are linkable through an encrypted but unique personal identification number, and thus, provide a longitudinal medical history of each individual. This study was exempted from full ethical review by the International Review Board, China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115).

Study population

We conducted the retrospective cohort study to determine the association between AS (ICD-9-CM code 720.0) and sleep disorders [ICD-9-CM codes 292.85 (drug induced sleep disorders), 307.4X (specific disorders of sleep of nonorganic origin), 327.

XX (organic sleep disorders), and 780.5X (sleep disturbances)]. From the LHID 2000, we identified patients aged ≥ 20 years with newly diagnosed AS during 2000−2010. The index date was the date of an initial diagnosis of AS. A comparison cohort was randomly selected among patients without AS, frequency matched on gender, age group (every 5 years), and index year based on a 1:4 ratio. In both cohorts, patients with a history of sleep disorders or with missing information such as gender or age were excluded.

Baseline variables

We obtained baseline variables, including gender, age, comorbidities of hypertension (ICD-9-CM codes 401−405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), heart failure (HF, ICD-9-CM code 428), cerebrovascular disease (CVA, ICD-9-CM code 430−438), chronic obstructive pulmonary disease and allied conditions (OPD, ICD-9-CM code 490−496), chronic liver disease and cirrhosis (CLD, ICD-9-CM code 571), chronic kidney disease (CKD, ICD-9-CM code 585), and anxiety and depression (ICD-9-CM code 296.2−296.3, 300.00, 300.4, 311).

Outcome measurement

The main outcome was the diagnosis with sleep disorders during the follow-up. Participants were followed from the index date to the diagnostic date of sleep disorders, the date of withdrawal from the insurance, to the point where they were censored because of death, or the end date of 2011. Only people with ≥ 3 times of coding were confirmed to have either AS, comorbidities, or sleep disorders in the present study.

Statistical analysis

All analyses were performed using an SAS statistical package (SAS System for Windows, Version 9.1.3, SAS Institute Inc., Cary, NC, USA). A p value of < 0.05 was considered statistically significant. Distribution of gender, age (20–34, 35–49, 50–64 and > 65), and comorbidities were compared between the AS cohort and the non-AS cohort, and were examined using the Chi-square test for categorical variables and t-test for continuous variables. The gender-, age-, and comorbidity-specific incidence of sleep disorders were estimated for both cohorts. Univariable and multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for sleep disorders in patients with AS in a relationship to the non-AS cohort. Baseline characteristics variables such as gender, age, and comorbidities were included in the multivariate model for adjustment. Because the comorbidities including hypertension, CVA, OPD, CLD, and anxiety and depression in the multivariable Cox model were significant, further data analysis was performed to evaluate the interaction pattern between AS and these comorbidity on sleep disorders risk. To compare the effect of different types of sleep disorders, we further classified it into OSA (ICD-9-CM code 327.23, 780.51, 780.53 and 780.57) and non-OSA sleep disorders. The cumulative incidence for sleep disorders between AS cohort and non-AS cohort was assessed using the Kaplan-Meier method, and the differences between the curves were tested with the log-rank test.

Results

The study includes a cohort of 1,785 subjects with AS and a non-AS cohort of 7,140 subjects (Table 1). Both cohorts had similar distributions of gender and age, and were predominantly male (64.7%) and less than 49 years of age (64.5%). Mean age for the AS and non-AS cohort was 44.7 [standard deviation (SD) = 16.8] and 44.4 (SD = 17.0) years, respectively. Comorbidities of hypertension, hyperlipidemia, OPD, CLD, and anxiety and depression were more prevalent in the AS cohort at the baseline (p <

Table 1. Demographic characteristics and comorbidity in subjects with and without ankylosing spondylitis

Variables	Ankylosing spondylitis				p-value†
	No (N = 7140)		Yes (N =1785)		
	n	%	n	%	
Sex					0.99
Male	4620	64.7	1155	64.7	
Female	2520	35.3	630	35.3	
Age, years					0.99
20–34	2528	35.4	632	35.4	
35–49	2076	29.1	519	29.1	
50–64	1452	20.3	363	20.3	
≥ 65	1084	15.2	271	15.2	
Mean (SD) †	44.4	(17.0)	44.7	(16.8)	0.53
Comorbidity					
Hypertension	1396	19.6	444	24.9	<0.001
Diabetes	397	5.56	111	6.22	0.28
Hyperlipidemia	849	11.9	298	16.7	<0.001
Heart failure	97	1.36	34	1.90	0.09
CVA	131	1.83	39	2.18	0.33
OPD	1346	18.9	457	25.6	<0.001
CLD	870	12.2	366	20.5	<0.001
CKD	57	0.80	13	0.73	0.76
Anxiety and depression	246	3.45	115	6.44	<0.001

CVA, cerebrovascular disease; OPD, chronic obstructive pulmonary disease and allied conditions; CLD, chronic liver disease and cirrhosis; CKD, chronic kidney disease;
Chi-square test; †Two sample t-test.

0.001), compared to the non-AS cohort. During the mean follow-up of 6.00 years for the AS cohort and 6.33 years for the non-AS cohort, the overall incidence of sleep disorders (per 1000 person-year) was 28.4 and 17.6, respectively (Table 2). Figure 1 shows the cumulative sleep disorders incidence curve for the two cohorts, and indicates that the incidence of sleep disorders in AS cohort is significantly higher than the non-AS cohort (log-rank test, $p < 0.001$). After adjusted age, sex and selected comorbidities, AS patients compared to subjects without AS, had a 1.47-fold higher risk of sleep disorders (95% CI = 1.29–1.68).

The sleep disorders incidence was greater in women than in men in both cohorts. The sex-specific AS cohort to non-AS cohort relative incidence of sleep disorders was significant for both men (adjusted HR = 1.35, 95% CI = 1.12–1.64) and women (adjusted HR = 1.62, 95% CI = 1.34–1.96). The incidence of sleep disorders increased with age in both cohorts. The age-specific analysis showed that AS patients had a greater incidence of sleep disorders development than the non-AS cohort in all age groups. The comorbidity-specific AS cohort to non-AS cohort adjusted HR of sleep disorders were significant for both without comorbidity (adjusted

Table 2. Incidences and hazard ratios of sleep disorders for ankylosing spondylitis cohort compared to non-ankylosing spondylitis cohort by demographic characteristics and comorbidity

Variables	Ankylosing spondylitis						Crude HR[#] (95%CI)	Adjusted HR[†] (95%CI)
	No (N = 7140)			Yes (N = 1785)				
	Event	Person years	Rate[$]	Event	Person years	Rate[$]		
Total	795	45178	17.6	304	10719	28.4	1.60(1.40, 1.83)***	1.47(1.29, 1.68)***
Sex								
Male	416	29433	14.1	148	7184	20.6	1.46(1.21, 1.76)***	1.35(1.12, 1.64)**
Female	379	15745	24.1	156	3535	44.1	1.80(1.49, 2.17)***	1.62(1.34, 1.96)***
p for interaction								0.11
Age, years								
20–34	176	16490	10.7	79	4013	19.7	1.84(1.41, 2.40)***	1.78(1.36, 2.34)***
35–49	252	13610	18.5	94	3218	29.2	1.56(1.23, 1.98)***	1.43(1.12, 1.82)**
50–64	195	9113	21.4	77	2096	36.7	1.69(1.30, 2.20)***	1.49(1.14, 1.96)**
≥ 65	172	5965	28.8	54	1392	38.8	1.33(0.98, 1.81)	1.20(0.88, 1.64)
p for interaction								0.18
Comorbidity[‡]								
Yes	367	28569	12.9	101	5436	18.6	1.44(1.16, 1.80)**	1.52(1.22, 1.90)***
No	428	16609	25.8	203	5283	38.4	1.49(1.26, 1.76)***	1.52(1.29, 1.80)***
p for interaction								0.81

Rate[$] per 1000 person-year; Crude HR [#], relative hazard ratio;

[†] Model was adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease and allied conditions, chronic liver disease and cirrhosis, chronic kidney disease, and anxiety and depression;

[‡] Patients with any one of the comorbidities (hypertension, diabetes, hyperlipidemia, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease and allied conditions, chronic liver disease and cirrhosis, chronic kidney disease, and anxiety and depression) were classified as the comorbidity group;

**p<0.01, ***p<0.001.

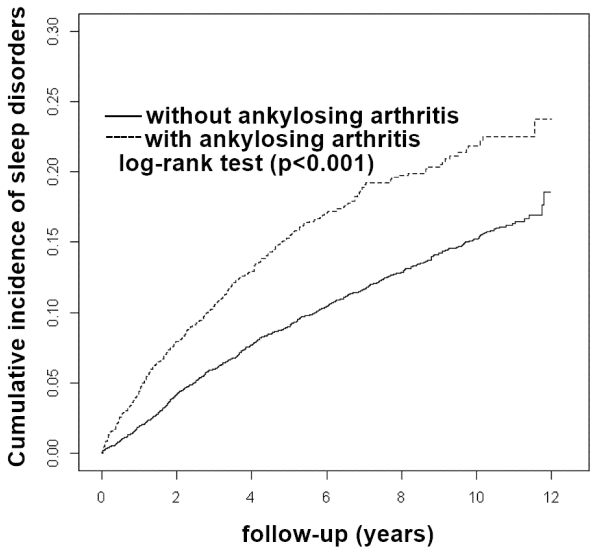

Figure 1. Cummulative incidence of sleep disorders between subjects with and without ankylosing spondylitis.

HR = 1.52, 95% CI = 1.22–1.90) and with comorbidity (adjusted HR = 1.52, 95% CI = 1.29–1.80).

We illustrated the interactions of AS and certain comorbidities on sleep disorders risk in Table 3. Compared with patients who lacked AS and anxiety and depression, patients with both AS and anxiety and depression demonstrated a significantly higher risk of sleep disorders (adjusted HR = 3.01, 95% CI = 1.16–7.83; interaction = 0.01). Compared to patients without AS and without CVA, AS patients with CVA had significantly increased risk of sleep disorders (adjusted HR = 2.71, 95% CI = 1.58–4.65). Table 4 shows AS associated with the relative risks and hazards of different types of sleep disorders. Compared with the non-AS cohort, patients with AS were 1.37-fold more likely to develop OSA (95% CI = 0.75–2.51), but this was not significant.

Discussion

To the best of our knowledge, this is the first nationwide, population-based study evaluating the relationship between AS and subsequent risk of sleep disorders. The present study results demonstrated an increased risk of sleep disorders in patients with AS, compared with those in the general population. The incidence of sleep disorders were greater in women than in men, in older than in younger people, and in those with comorbidities. These findings are in accordance with the general concepts. We also found that certain comorbidities were more prevalent in AS population which the phenomenon was considered to be associated with chronic inflammation.[13–17] In addition, patients with AS had a higher incidence of OSA than those without AS, but this was not significant. We suggest that AS may play an independent role in the development of sleep disorders.

Various sleep problems, including poor quality of sleep, sleep onset insomnia, difficulty awakening, and OSA, have been reported in AS.[18] Sleep disturbance induced by axial pain and stiffness in the latter half of the night is a specific characteristic in patients with AS.[19] In addition to the inflammatory pain, a possible role for cytokines in the regulation of sleep was addressed in patients with systemic inflammatory disorders.[20, 21] As we know, people with other inflammatory diseases also have an increased risk of sleep disorders.[22, 23] Sleep disturbance can reduce an individual's quality of life by seriously impairing cognition, mood, and symptoms of disease. Several studies revealed sleep disturbance was associated with more frequent attention deficit, difficulty in learning and memory consolidation, difficulty in coping with stressful life events, decreased academic performance, reduced neurobehavioral functioning, and moreover, decreased threshold of pain.[24–26] Therefore, sleep disturbance could cause a negative impact on exercise, rehabilitation, and daytime life in patients with AS.

Assessing sleep disturbance in patients with AS is a very important concern. Several studies reported sleep disturbance in patients with AS was associated with increased pain, disease activity and parameters, psychological status, and quality of life.[8–10] In addition, Heiberg et al.[27] reported sleep

Table 3. Cox proportional hazard regression analysis for the risk of sleep disorders -associated ankylosing spondylitis with interaction of comorbidity

Variables		N	Event n	Adjusted HR† (95% CI)	p-value‡
Ankylosing spondylitis	Hypertension				
No	No	5744	560	1(Reference)	0.21
No	Yes	1396	235	1.32(1.09, 1.59)**	
Yes	No	1341	204	1.57(1.34, 1.85)***	
Yes	Yes	444	100	1.69(1.32, 2.15)***	
Ankylosing spondylitis	CVA				
No	No	7009	773	1(Reference)	0.61
No	Yes	131	22	1.60(1.04, 2.47)*	
Yes	No	1746	290	1.47(1.29, 1.69)***	
Yes	Yes	39	14	2.71(1.58, 4.65)***	
Ankylosing spondylitis	OPD				
No	No	5794	585	1(Reference)	0.51
No	Yes	1346	210	1.31(1.11, 1.55)**	
Yes	No	1328	204	1.54(1.32, 1.81)***	
Yes	Yes	457	100	1.77(1.42, 2.21)***	
Ankylosing spondylitis	CLD				
No	No	6270	646	1(Reference)	0.19
No	Yes	870	149	1.61(1.34, 1.93)***	
Yes	No	1419	222	1.55(1.33, 1.80)***	
Yes	Yes	366	82	2.09(1.64, 2.65)***	
Ankylosing spondylitis	Anxiety & Depression				
No	No	6894	732	1(Reference)	0.01
No	Yes	246	63	3.60(1.42, 9.16)**	
Yes	No	1670	277	1.56(1.36, 1.79)***	
Yes	Yes	115	27	3.01(1.16, 7.83)*	

CVA, cerebrovascular disease; OPD, chronic obstructive pulmonary disease and allied conditions; CLD, chronic liver disease and cirrhosis;
† Model was adjusted for age and sex;
‡ p-value for interaction;
*p<0.05, **p<0.01, ***p<0.001.

Table 4. Incidences and hazard ratios of different type of sleep disorders for ankylosing spondylitis cohort compared to non-ankylosing spondylitis cohort

Variables	Ankylosing spondylitis				Crude HR # (95%CI)	Adjusted HR† (95%CI)
	No (N = 7140)		Yes (N = 1785)			
	Event	Rate$	Event	Rate$		
Obstructive sleep apnea	40	0.89	15	1.40	1.57(0.86, 2.83)	1.37(0.75, 2.51)
Non-OSA sleep disorders	788	17.4	302	28.2	1.61(1.41, 1.83)***	1.47(1.29, 1.69)***

OSA, obstructive sleep apnea; Rate$ per 1000 person-year; Crude HR #, relative hazard ratio;
† Model was adjusted for age, sex and comorbidities of hypertension, diabetes, hyperlipidemia, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease and allied conditions, chronic liver disease and cirrhosis, chronic kidney disease, and anxiety and depression;
***p<0.001.

problems are a higher priority for improvement to patients with AS than for patients with other inflammatory arthropathies. They found patients with AS reported priority for improvement in sleep problems significantly more frequently than rheumatoid arthritis, psoriatic arthritis, and juvenile inflammatory arthritis in adult age. Moreover, there was several studies that concluded that treatment effects of anti-tumor necrosis factors (anti-TNF) for AS were based on improved sleep disturbance, which was taken as an essential parameter of disease activity.[28–30]

There are few studies that mentioned the relationship between OSA and AS. Erb et al.[31] reported a higher prevalence of sleep apnea syndrome in patients with AS (12%) than has been reported in the general population (1–4%). They suggested sleep apnea syndrome as a cause of fatigue in AS. Another report by Solak et al.[32] revealed 22.6% (7/31) patients with AS had OSA, according to polysomnography assessment. They concluded OSA should be kept in mind especially in AS patients at the age of >35 years and with a disease duration >5 years. The possible mechanisms of OSA in AS patients included restriction of the oropharyngeal airway from temporomandibular joint involvement, pharyngeal and tracheal compression by cervical spine disease, or restrictive pulmonary disease.[31] In the present study, we showed the overall incidence rate of OSA was 57% greater in the AS cohort than in the non-AS cohort (1.40 vs. 0.89 per 1000 person-year), with an adjusted hazard ratio of 1.37 (95% CI = 0.75–2.51).

The incidence reported here appeared less, probably because of the present study reflecting a relative “real world” scenario, where the diagnoses of sleep disorders are because of a real medical consultation. Thus, the patients with sleep disorders included were believed to have greater disease severity. In addition, the participants in the previous studies passively received and answered a questionnaire. Not surprisingly, the prevalence of sleep disorders in the AS group has been reported to be as high as 59–65%.[8, 10] Nevertheless, we consider that sleep disorders is indeed a greatly underestimated problem in AS patients. Clinical physicians should pay more attention to this group of individuals and provide appropriate support.

A major strength of our study is that it was performed using population-based data that are highly representative of the general population. However, certain limitations should be considered. First, the NHIRD does not contain detailed information regarding smoking habits, diet preference, occupational exposure, drug history, and family history of systemic diseases, all of which may be risk factors for AS and sleep disorders. Second, evidence derived from a retrospective cohort study is generally lower in statistical quality than that from a randomized trial because of potential biases associated with adjustments for confounding variables. Despite our meticulous study design and adjustment for confounding factors, biases resulting from unknown confounders may have affected our results. Third, all data in the NHIRD are anonymous. Therefore, relevant clinical variables such as serum laboratory data, polysomnography, and imaging results of the subjects were unavailable in our study.

Conclusion

AS patients had a significantly higher risk of developing sleep disorders than the general population. The incidence of OSA in AS patients was also higher; however, it was not statistically significant.

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僵直性脊椎炎和後續睡眠疾患的風險：一個以台灣人口為基礎的回溯性世代研究

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摘 要

僵直性脊椎炎病患合併有睡眠疾患的情形相當普遍；然而，大型的、以人口學為基礎的研究卻闕如。我們利用台灣的一個全國性資料庫來檢驗僵直性脊椎炎病患及其後續發生睡眠疾患的風險。我們利用台灣的健保資料庫設計了一個回溯性的世代研究，病例群組包含了1,785位自2000至2010年被新診斷為僵直性脊椎炎的病人。診斷日期被定義為指示日期。每一位病人根據年齡、性別與指示日期隨機分配四位對照個案作為控制群組。睡眠疾患的發生由指示日期開始追蹤到2011年底。僵直性脊椎炎群組比控制群組發生睡眠疾患的比例整體高出1.60倍 (每千人年為28.4比17.6)，校正後的風險比值是1.47 (95% 信賴區間為1.29-1.68)。此外，我們發現阻塞性睡眠呼吸中止症的發生率亦在僵直性脊椎炎群組比起控制群組來得要高，但並沒有達到統計學上有意義的程度。此一研究顯示患有僵直性脊椎炎的病患比起一般人口有較高的風險罹患睡眠疾患。阻塞性睡眠呼吸中止症的發生率亦較高，然而並沒有達到統計學上的顯著程度。