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Increased risk of ankylosing spondylitis after *Mycoplasma pneumonia*
A Nationwide population-based study

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Abstract
This study aimed to investigate the relationship between *Mycoplasma pneumonia* (MP) infection and new development of ankylosing spondylitis (AS).

Using data from the Taiwan National Health Insurance Research Database, we included a total of 116,084 patients with newly diagnosed MP between 2000 and 2012. The control cohort consisted of patients who did not have MP, matched 1:4 by age, sex, and index year. The follow-up period was defined as the time from the initial diagnosis of MP to the date of diagnosis of AS, censoring, or 31 December 2013. Cox proportional hazards regression analysis was used to analyze the risk of autoimmune diseases by sex, age, and comorbidities, with hazard ratios (HRs) and 95% confidence intervals (CIs).

The eligible study participants included 116,084 patients in the MP group and 464,336 patients in the comparison group. The incidence rates of AS in the MP group and comparison groups were 1.49 and 0.74 per 1,000,000-person years, respectively. The adjusted HR of AS for the MP group was 2.45 (95% CI = 1.02−5.90) compared to the control group after adjustment for age, sex, and all covariates.

MP remained an independent risk factor for developing AS in terms of sex, age, and comorbidities.

Abbreviations: AS = ankylosing spondylitis, 95% CI = 95% confidence interval, HR = hazard ratio, MP = *Mycoplasma pneumonia*, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, SpA = spondyloarthropathy.

Keywords: ankylosing spondylitis, *Mycoplasma pneumonia*, population-based cohort study

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1. Introduction

Autoimmune diseases are part of the major causes of death in women younger than 65 years in the United States,[1] England, and Wales[2] and are also the top causes of morbidity in women in the United States.[1,3] In addition, autoimmune diseases have been reported to be increasing in the United States and all over the world, making themselves an important public health issue at levels similar to malignancy and heart disease.[4] What makes it worse is that too little is known about what are the most important triggering factors in autoimmune diseases.[4] Of the environmental factors, infections play a major role in the development of autoimmune diseases, and viruses, bacteria, and other infectious microorganisms are considered to be major triggers of autoimmunity.[5–7]

Of all the autoimmune diseases, reactive arthritis is conventionally defined as an arthritis that arises after an infection process, although mostly the pathogens have not been cultured from the affected joint specimens. It is generally regarded as a form of spondyloarthropathy (SpA).[8] Ankylosing spondylitis (AS) is the prototypic SpA, characterized by prominent axial skeletal involvement, including sacroiliitis, and enthesitis.[9–11] Reactive arthritis has been sporadically reported as triggered by *Mycoplasma pneumonia* (MP) before.[12,13] Further findings in later study provided clear evidence of reactive arthritis diagnosis following an acute MP infection that in 4 patients progressed to chronic juvenile SPA.[14] The long-term effects of MP infection are yet to be determined. A significant lack of epidemiological studies of autoimmune arthritis such as AS may greatly increase the difficulty of developing future monitoring for infections of high prevalence such as MP, which is the second most common causative pathogen of community-acquired pneumonia for adults in Taiwan.[15]

Because of a lack of research on the epidemiological relationship between MP infection and the subsequent

development of AS, we conducted the longitudinal nationwide cohort study to explore whether patients infected with MP are prone to the subsequent development of AS.

2. Materials and methods

2.1. Data source

In this retrospective cohort study, we used reimbursement claims data retrieved from the Taiwan National Health Insurance Research Database (NHIRD). Taiwan has implemented a nationwide compulsory health insurance program since 1995, and it currently covers >99% of Taiwan's population. Data in the NHIRD include inpatient expenditure by admission and the inpatient records of all beneficiaries enrolled in the National Health Insurance (NHI) program. For the patients' privacy, their identity is encrypted before being released by the National Research Institutes. This study was approved by the Institutional Review Board, China Medical University, and Hospital Research Ethics Committee (IRB permit number: CMUH-104-REC2-115).

2.2. Study participants

We used Taiwan NHIRD for this study. In Taiwan, the protocol for diagnosing MP is relatively well established[16] and our hospitals have the certified disease-coding expertise to complete the accurate International Classification of Diseases (ICD) coding before submitting medical claims data to the Bureau of NHI. From inpatients claim dataset, we identified all hospitalized patients infected with MP (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 483.0) from 2000 to 2012. The index date was defined as the date of a diagnosis of MP. Patients with a history of AS (ICD-9-CM code 720.0) before the index date and those with incomplete age or sex information were excluded. For the comparison group, we randomly selected from inpatients who had never been diagnosed with MP and AS with a ratio of 4:1 to the MP group matched by age, sex, and index year.

2.3. Outcome and relevant variables

The main outcome was hospitalization with a new diagnosis of AS during the follow-up period. In Taiwan, patients who fulfill the 1984 modified New York criteria for AS are defined in NHI database as AS. The patients were followed until a diagnosis of AS, withdrawal from the NHI program, or the end of 2013, whichever occurred first. The comorbidities analyzed in this study were hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (CAD, ICD-9-CM codes 410-414), chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 491, 492, 496), asthma (ICD-9-CM code 493), cancer (ICD-9-CM codes 140-208), allergic rhinitis (ICD-9-CM codes 477, 472.0), atopic dermatitis (ICD-9-CM code 691), chronic liver diseases (ICD-9-CM code 571.4), hepatitis B (ICD-9-CM codes 070.2, 070.3, V02.61), and hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, V02.62).

2.4. Statistical analysis

The chi-squared test was used for category variables and t test for continuous variables. Person-years was calculated from the sum of the follow-up time for each individual, and the follow-up time was defined as the period from the index date to the diagnosis of AS, withdrawal from the NHI program, or the end of 2013. The incidence rate was calculated according to the number of occurrences and person-years. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the 2 groups were estimated using univariate and multivariate Cox proportional hazard regression models. The variables in the multivariate model included age, sex, and all comorbidities. SAS statistical software (version 9.4 for Windows; SAS Institute Inc., Cary, NC) was used for data analysis, and a P value <.05 was considered to indicate statistical significance.

3. Results

3.1. Demographic characteristics and comorbidities of the patients with Mycoplasma pneumonia and the comparison cohort

The eligible study participants included 116,084 patients in the MP group and 464,336 patients in the comparison group. There were no significant differences in age and sex between the 2 groups (Table 1). There were more women (52.0%) than men, and most of the patients were aged ≤19 years (85.5%). The MP group had a higher incidence rate of comorbidities. The mean follow-up times in the MP and comparison groups were 5.19 and 5.21 years, respectively.

3.2. Comparison of the incidence and HR of AS stratified by sex and age of the patients with Mycoplasma pneumonia and the comparison cohort

The incidence rates of AS in the MP and comparison groups were 1.49 and 0.74 per 1,000,000-person years, respectively. Compared with the comparison group, the adjusted HR of AS for the MP group was 2.45 (95% CI = 1.02–5.90) compared to the control group (Table 2). Compared to the women without MP, the crude HR of AS for the MP group was 3.96 (95% CI, 0.99, 15.8) compared with the control group (P = .05). After adjusting by age, and all comorbidities, the adjusted HR for the female MP group was 3.74 (95% CI, 0.80–17.5, P = .09) compared to the female control group.

4. Discussion

Our current study is the first population-based epidemiological study to investigate the relationship between MP and future risk of developing AS. Results of our nationwide matched cohort study revealed that, as compared to the general population, the patients with MP had a 2.45-fold higher risk of AS. Although the patients with MP had a higher rate of comorbid diseases compared to the comparison cohort, MP remained an independent risk factor for developing AS in terms of sex, age, and comorbidities.

Although multiple factors are thought to contribute to the development of autoimmune diseases, previous immunological studies on animal models of autoimmune diseases strongly suggested that infections accounted for the major environmental factors triggering human autoimmune diseases,[17,18] despite the fact that so far such relevant human data are unavailable.

Mycoplasmas are ubiquitous in the world and are the smallest bacteria that can survive alone in nature.[19,20] Some of the species have been documented to be associated with reactive

Table 1

Baseline characteristics of patients.

| | *Mycoplasma pneumonia* | | | | | |
| | Yes (n=116,084) | | No (n=464,336) | | | |
	n	%	n	%	P*	
Sex					>.99	
Male	55,726	48.0	222,904	48.0		
Female	60,358	52.0	241,432	52.0		
Age					>.99	
≤19	99,251	85.5	397,004	85.5		
20–39	7049	6.07	28,196	6.07		
40–64	4927	4.24	19,708	4.24		
≥65	4857	4.18	19,428	4.18		
Mean (SD)	12.0 (18.0)		12.0 (18.0)		.91	
Comorbidity						
Hypertension	4830	4.16	8270	1.78	<.0001	
Diabetes mellitus	2825	2.43	4261	0.92	<.0001	
Hyperlipidemia	1426	1.23	2033	0.44	<.0001	
CAD	2302	1.98	3875	0.83	<.0001	
Hepatitis B	627	0.54	545	0.12	<.0001	
Hepatitis C	479	0.41	432	0.09	<.0001	
Cancer	858	0.74	2432	0.52	<.0001	
Allergic rhinitis	7429	6.40	3182	0.69	<.0001	
Chronic liver diseases	436	0.38	423	0.09	<.0001	
Atopic dermatitis	7470	6.43	9577	2.06	<.0001	
Asthma	19,381	16.7	10,411	2.24	<.0001	
COPD	2993	2.58	2134	0.46	<.0001	

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease.

* Chi-square test.

† t test

arthritis.[12–14,21] Poggio et al studied 33 hospitalized pediatric patients in Argentina who had joint disorders and found that *M hominis* and *Ureaplasma urealyticum* were isolated from 3% and 1% of joint fluid samples, respectively. MP had been isolated from nasopharyngeal secretion in a patient with evidence of a reactive arthritis.[12] Their results raise the question of the possible role of *Mycoplasma* as a cofactor in the triggering of inflammatory joint disease.[12] Johnson et al[21] investigated synovial fluid samples which collected from the knee joints of different arthritis patients in United Kingdom and found *M fermentans* was detected in the synovial fluid of one patient with reactive arthritis, one patient with pauciarticular juvenile chronic arthritis, and 2 patients with AS, but was not detected in any of the patients with osteoarthritis . Harjacek et al evaluated the potential relationship between the acute MP infection and juvenile SpA in 12 children with reactive arthritis secondary to acute MP. It was noted that 3 patients developed enthesitis-related arthritis, and in 1 patient, genuine juvenile AS was

Table 2

Incidence and hazard ratio of ankylosing spondylitis for *Mycoplasma pneumonia* patients compared to controls stratified by sex, age, and comorbidity.

| | *Mycoplasma pneumonia* | | | | | | Compared to Control | | | |
| | Yes | | | No | | | Crude | | Adjusted | |
	Event	PY	IR	Event	PY	IR	HR (95% CI)	P	HR (95% CI)	P
Overall	9	602,540	1.49	18	2,419,878	0.74	2.00 (0.90,4.45)	.09	2.45 (1.02,5.90)	.046
Sex										
Male	5	287,651	1.74	14	1,161,416	1.21	1.44 (0.52,3.99)	.48	2.03 (0.67,6.10)	.21
Female	4	314,889	1.27	4	1,258,462	0.32	3.96 (0.99,15.8)	.05	3.74 (0.80,17.5)	.09
Age										
≤19	2	535,760	0.37	5	2,130,401	0.23	1.57 (0.30,8.07)	.59	1.21 (0.21,7.07)	.83
20–39	3	33,880	8.85	4	135,170	2.96	2.98 (0.67,13.3)	.15	2.11 (0.42,10.7)	.37
40–64	3	19,947	15.0	4	85,977	4.65	3.19 (0.71,14.3)	.13	3.34 (0.59,19.0)	.17
≥65	1	12,952	7.72	5	68,331	7.32	1.07 (0.12,9.16)	.95	1.78 (0.19,16.6)	.61
Comorbidity§										
No	4	428,738	0.93	14	2,268,196	0.62	1.50 (0.49,4.56)	.47	2.12 (0.68,6.61)	.20
Yes	5	173,802	2.88	4	151,682	2.64	1.13 (0.30,4.20)	.86	3.10 (0.71,13.6)	.13

Model was adjusted by sex, age, and all comorbidities listed in Table 1.

Comorbidity: Patients with any one of the comorbidities were classified as the comorbidity group.

CI = confidence interval HR = hazard ratio, IR = incidence rate, per 1,000,000-person years, PY = person-years.

diagnosed.[14] In a recent national case-control study from Sweden with 2453 cases of AS and 10,257 controls, approximately 17.4% of the AS cases and 16.3% of the controls had been hospitalized with an infection before the age of 17 years, although the overall infections did not reach a significant higher risk of AS (adjusted hazard ratios [aOR] 1.08, 95% CI 0.96–1.22). History of past respiratory tract infections were, however, significantly higher in AS group (11.2%) than the control group (9.2%) with aOR 1.24, 95% CI 1.07 to 1.44. Of notes, history of tonsillitis were (cases 3.7%; controls 2.8%; OR 1.31, 95% CI 1.03–1.67) most associated with AS. They concluded that childhood respiratory tract infections (especially tonsillitis) were associated with an increased risk for later development of AS. Their infections cases were limited to infections resulting in inpatient care. On the contrary, our study is a cohort study design with 13-year follow-up, indicating a better temporal relationship between MP exposures and the development of AS. But we also only enrolled hospitalized patients infected with MP; therefore, less severe forms of MP was excluded.

The mechanism by which MP increases the risk of developing AS is not clear till now, but some previous studies to animal models can provide the possible hints. *Mycoplasma* species could cause acute or chronic arthritis in different animal species in rats, mice via one of the "superantigens," that activates T cells expressing many different beta genes.[22–24] *Mycoplasmas* also demonstrated great effects on immune cells and the immune system of the host, including polyclonal activation of T and B cells and the associated secretion of cytokines.[24] However, it remains uncertain whether they elicit the immunopathological process through molecular mimicry or modulation of the immune response via immune cell activation and cytokine production causing a cytokine imbalance.[14,25]

This nationwide cohort study has the strength of enrolling a large number of participants, and longer duration of follow-up period and the results are robust because multivariable analyses were used for assessing the increased risk of AS development. Studies indicating a temporal relationship between environmental exposures and the development of AS are rare. Our nationwide population-based cohort study demonstrated a higher risk (aHR 2.45, 95% CI 1.02–5.90) of AS in patients with MP. This new information can add to the literature because previous case-control study revealed a possible relationship between childhood respiratory tract infections and later development of AS. This study can provide implications for current practice. Clinically, physicians and patients should be aware of this possible association. In managing patients with history of MP with back pain or arthritis, physicians should raise their alert on AS and may consider additional tests such as x-rays of the sacroiliac joints or HLA-B27 check-up.

5. Limitations

There are also some limitations deserving attention. First, the NHIRD does not provide detailed information such as smoking habits, body mass index, socioeconomic status, inflammatory biomarkers, and family history, all of which are potential confounding factors in this study. Second, the study cases were selected according to ICD-9-CM codes, which may potentially cause a misclassification bias despite the ability of the auditing mechanism used by the Bureau of NHI to minimize diagnostic uncertainty and misclassification.[26] However, the NHI claim database is an established research database and there have been some independent studies demonstrating the validity of the NHIRD data.[27,28] Third, our study only enrolled hospitalized patients infected with MP; therefore, less severe forms of MP was excluded. Finally, since Taiwanese are mainly of Chinese ethnicity, it is uncertain whether our findings can be generalized to other ethnic groups. Our findings, therefore, should be interpreted with caution given some methodological flaws such as the absence of data on important inflammatory biomarkers, family history, and MP severity measurement.

6. Future directions

Future studies, especially on pathogenesis of interaction between MP and AS should be done.

7. Conclusions

This 13-year population-based cohort study demonstrated a higher risk of AS in patients with MP. Clinicians are suggested to be alert on risk of AS in patients with MP and to provide appropriate tests.

Author contributions

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