Association Between Mycoplasma Pneumonia and Increased Risk of Ischemic Stroke

A Nationwide Study

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Background and Purpose—Infections have been hypothesized to play a role in vascular disease. The association between Mycoplasma pneumoniae (MP) infection and ischemic stroke remained undetermined.

Methods—A total of 1094 patients with MP infection were enrolled as the study group and compared with 5168 sex-, age-, and comorbidity-matched subjects without MP, to be followed up prospectively from January 2003 to December 2007 for development of ischemic stroke.

Results—During a maximum 5-year follow-up period, 49 patients with ischemic stroke were identified. Subjects with MP infection were significantly associated with increased risk of ischemic stroke compared with controls (1.10% versus 0.72%, respectively; $P=0.01$). The logrank test showed that patients with MP had significantly higher incidence of stroke development than did those without MP ($P=0.046$). After Cox model adjustment for risk factors and comorbidities, MP infection was still independently associated with increased risk of stroke (hazard ratio [HR], 2.07; 95% CI, 1.05–4.03).

Conclusions—We conclude that MP infection is independently associated with risk of subsequent ischemic stroke development. **(*Stroke*. 2011;42:2940-2943.)**

Key Words: inflammation ■ mycoplasma pneumoniae ■ ischemic stroke

Stroke is one of the most common causes of death worldwide and the leading cause of long-term disability. Recently, accumulating evidence has showed that atherosclerosis is not just a cholesterol storage disorder in vasculature, but is a sustained, dynamic, and chronic inflammatory process. Bacterial or viral infectious pathogens such as Chlamydia pneumoniae, Herpes zoster, and Cytomegalovirus have been reported to be associated with the occurrence of stroke.[1,2]

Mycoplasma pneumoniae (MP) infection, which was responsible for 32.5% of all community-acquired pneumonia in 1 study,[3] causes respiratory tract symptoms endemically and epidemically in all ages. Central nervous system involvement is probably the most serious extrapulmonary manifestation of infection. Although some studies identified that MP presented in atherosclerotic plaque,[4] and identified serological antibody for MP in patients with coronary artery disease,[5] the association between MP infection and cardiovascular events still remains undetermined. The aim of our study was to use a nationwide population prospectively to evaluate the association between MP infection and risk of ischemic stroke.

Methods

The National Health Insurance (NHI) program has been in operation since 1995 and includes 99.5% of the population in Taiwan. The NHI Research Database contained the complete NHI claims and has released a cohort data set made of 1 000 000 randomly sampled people. It is also 1 of the largest nationwide population-based databases in the world and has published several dozen extracted data sets for researchers.[2,6,7]

Patients with MP infections were enrolled: (1) men age ≥18 years old, and (2) patients who were diagnosed per the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 483.0 since January 1, 2003. The following patients were excluded: (1) patients who had been diagnosed with MP before January 1, 2003, or (2) patients who had been diagnosed with ischemic stroke (ICD-9-CM codes 434–438) before enrollment. The age, sex, time of enrollment, and comorbidities such as diabetes, hypertension, hyperlipidemia, and atrial fibrillation were matched between these 2 groups.

Stroke Event Measurement

The occurrence of ischemic stroke was identified by insurance claim. To avoid mistaken diagnoses, we only enrolled patients who had at least 2 administrative claims coded for ischemic stroke to avoid

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Table 1. Demographic Data of the Study Population

Characteristic	Mycoplasma Pneumonia		
	No (n=5168)	Yes (n=1094)	*P*
Age, y	40.6±15.5	40.2±15.1	0.351
Male, n (%)	2197 (42.5)	471 (43.1)	0.521
Hypertension, n (%)	765 (14.8)	163 (14.9)	0.870
Diabetes, n (%)	381 (7.4)	82 (7.5)	0.778
Dyslipidemia, n (%)	717 (13.9)	149 (13.6)	0.658
Chronic kidney disease, n (%)	99 (1.9%)	33 (3.0)	<0.001
Coronary artery disease, n (%)	234 (4.5)	61 (5.6)	0.003
Heart failure, n (%)	46 (0.9)	20 (1.8)	<0.001
Ischemic stroke outcome, n (%)	37 (0.72)	12 (1.10)	0.01

Data are mean±standard deviation (SD) or n (%).

administrative misdiagnosis of a single coding of stroke without subsequent neurologist follow-up. Furthermore, the stroke event was identified according to any 1 of the following conditions: (1) hospitalization claims or (2) >3 consecutive outpatient visits to hospitals; followed either by claims for various neurological imaging technology (computed tomography, magnetic resonance imaging, or transcranial or carotid Doppler sonography) and long-term prescriptions used for ischemic stroke; or (3) by claims for rehabilitation and the long-term ischemic stroke prescriptions. The sensitivity and specificity for ischemic stroke identification were 100% and 95%, respectively[6]; similar definition of stroke and more details have been described in our previous studies.[7] The identification of stroke using insurance claim was valid and used in a similar study.[7]

Statistical Analysis

Microsoft SQL Server 2005 (Microsoft Corporation) and SPSS software (SPSS Inc.) were used for data management and computing. Continuous data between groups were compared by Student *t* test. Categorical data were analyzed with Chi-square test and Yate's correction or Fisher's exact test as appropriate. Analysis of freedom from ischemic stroke was assessed using Kaplan–Meier analysis. Cox proportional hazards regression was performed to determine independent factors for stroke. In this cohort study, we aimed to investigate the association between baseline MP infection and future onset of stroke events during the 5-year follow-up period. Because time duration is critical in this study, the Cox regression model rather than logistic regression was applied to analyze the association. Statistical significance was inferred at a 2-sided probability value of <0.05.

Results

Table 1 shows demographic parameters of the subjects with MP, and age-, sex-, and stroke-related, comorbidity-matched controls. Although there were no significant differences in age, sex, hypertension, diabetes, atrial fibrillation, and dyslipidemia between these groups, subjects with MP still had higher prevalence of chronic kidney disease (1.9% versus 3.0%; $P<0.001$), coronary artery disease (4.5% versus 5.6%; $P=0.003$) and heart failure (0.9% versus 1.8%; $P<0.001$). During an average follow-up period of 2.13 years (maximum 5 years), 49 patients with ischemic stroke were identified. Subjects with previous MP infection were significantly associated with increased risk of ischemic stroke compared with controls (12 patients [1.10%] versus 37 patients [0.72%], respectively; $P=0.01$). The logrank test showed that patients with MP infections had significantly higher incidence of stroke development than did those without MP ($P=0.046$; Figure). After Cox proportional-hazard model analysis adjustment for age, sex, and comorbidity, only MP infection (hazard ratio [HR], 2.07; 95% CI, 1.05–4.03), diabetes (HR, 2.74; 95% CI, 1.36–5.53), hypertension (HR, 2.08; 95% CI, 1.27–3.51), and age (HR, 1.07; 95% CI, 1.05–1.09) were independently associated with increased risk of ischemic stroke (Table 2).

Discussion

Our current study is the first population-based epidemiological study to investigate the association between MP infection and risk of ischemic stroke. Although the actual mechanism of MP infection leading to atherosclerotic events remains undetermined, inflammatory process and persistently increased thromboembolic potential after MP infection seem to play an important role. MP has been found in atherosclerotic plaques,[4] and increased serum antibody of MP in patients

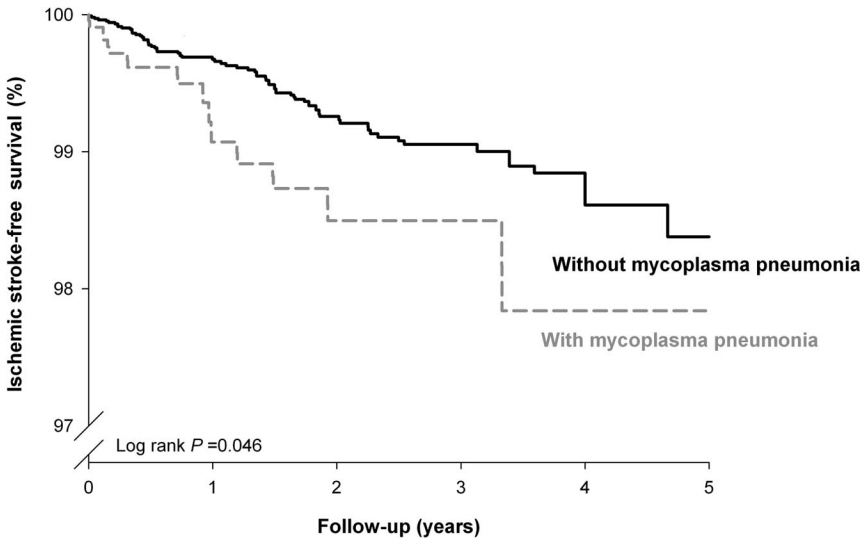

Figure. Kaplan–Meier estimates of survival free of ischemic stroke events in subjects categorized by mycoplasma pneumonia. The ischemic stroke-free survival rates were significantly different in the 2 groups ($P=0.046$ by log-rank test).

Table 2. Independent Predictors of Ischemic Stroke Identified by Cox Regression Analysis

Predictor	Hazard Ratio	95% CI	*P*
Mycoplasma pneumonia	2.07	1.06–4.03	0.032
Diabetes	2.74	1.36–5.53	0.005
Hypertension	2.08	1.27–3.41	0.004
Age, y	1.07	1.05–1.09	<0.001
Male sex	1.18	0.67–2.10	0.204
Dyslipidemia	1.39	0.65–2.99	0.395
Coronary artery disease	1.44	0.67–3.09	0.354
Congestive heart failure	1.00	0.99–1.007	0.656
Chronic kidney disease	0.80	0.23–2.78	0.729
Atrial fibrillation	0.97	0.10–9.28	0.979

CI indicates confidence interval.

with coronary artery disease has been reported,[5] suggesting a close relationship between MP and atherosclerosis. Leonardi et al proposed that MP infection-related ischemic stroke can be divided into early (parainfectious) and late (postinfectious) types, which directly involve the central nervous system or relate to immune reaction.[8] MP has been isolated from the cerebrovascular fluid of stroke patients,[9] and it may induce chemokines such as TNF-α[10] and IL-8[11] in vasculature, which cause local vasculitic or thrombotic vascular occlusion. Furthermore, MP infection can induce a systemic hypercoagulable state.[12] Altogether, MP infection may contribute to stroke risk through direct central nervous system invasion, immune mechanism, vascular occlusion, and hypercoagulable state.

Our study is the first population-based epidemiological study to investigate the association between MP infections, and the strength of our study is the use of a population-based data set, which enrolled a large sample of subjects, enabling us to trace prospectively the differences between the 2 groups. However, there are still some limitations to our study. First, the diagnosis of MP and stroke were identified using the ICD-9 code from the database. Personal information such as body weight, smoking habits, and biochemistry profiles were not available. This study was conducted with NHI database, in which diagnosis was supposed to be confirmed clinically by the individual physicians in charge. However, it is not known whether the diagnosis of MP was made based on results of serum examinations like ELISA, antibody test, or polymerase chain reaction in each individual case. It was also not checked externally in our study. Second, in this study, a 2-step approach was used to define the events of stroke. In the first, by enrolling subjects who had at least 2 coding for ischemic stroke, we tried to avoid administration misdiagnosis of a single coding of stroke without subsequent neurologist follow-up. In the second, the individual stroke event could be established and identified only if there were any 1 of the following conditions: (1) hospitalization claims, or (2) more than 3 consecutive outpatient visits to hospitals; followed either by claims for various neurological imaging technology (computed tomography, magnetic resonance imaging, or transcranial or carotid Doppler sonography) and long-term prescriptions used for ischemic stroke, or (3) by claims for rehabilitation and the long-term ischemic stroke prescriptions. We had previously defined the sensitivity (100%) and specificity (95%) to identify the event of ischemic stroke with the above approach in another cohort study.[6,7] However, we could not completely exclude the possibility of misdiagnosis, as institutions treating the patients later after stroke often just carry the initial diagnosis forward. It is one of the major limitations in this type of study with the NHI database. Third, in this cohort study, we tried to investigate the association between baseline MP infection and future onset of stroke events during the follow-up period. Because time duration is critical in this study, the Cox regression model rather than logistic regression was applied to analyze the association. The results of logistic regression showed a trend, but not significant association between MP and stroke (crude odds ratio, 1.538; 95% CI, 0.799–2.959; adjusted odds ratio, 1.496; 95% CI, 0.766–2.38) similar to that in the Cox regression model. We think that the results may be reasonable given that fewer time issues were involved in the logistic regression model. Atherosclerosis is now considered a chronic inflammatory disease, and the study subjects were relative young in our study (average age, 40 years). Therefore, the impact of time interval between MP infection and primary end point is critical. Although the results of logistic regression showed an insignificant trend, the results of Cox regression demonstrated the association of MP infection with increased future risk of ischemic stroke, suggesting that time duration should be taken into consideration for clinical risk stratification of future stroke by MP infection. Finally, because the study subjects were young in our study and the annual incidence of stroke in Taiwanese people of this age might be less than 0.03%,[13] a larger sample might be required in each group. Therefore, all subjects who fit inclusion criteria from the database were enrolled, in which MP could be independently associated with the risk of stroke. Because a relatively low number of events were recorded, although statistically significant, the clinical relevance needs to be established further. Larger sample-size populations in different ancestry groups are still needed for additional confirmation.

Disclosures

None.

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