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EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Allergic rhinitis and risk of erectile dysfunction – a nationwide population-based study

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Abstract

Background: A growing body of evidence has disclosed that allergic rhinitis (AR) is a systemic inflammatory disease. Inflammatory mediators and cells involved in AR have also been reported to be implicated in the process of atherosclerosis, which is relevant to the occurrence of erectile dysfunction (ED). Our objective was to explore the relationship between AR and future ED events.

Methods: From 1 January 2000 to 31 December 2008, we identified male patients, who were aged 18–55 years and newly diagnosed with AR from the Taiwan National Health Insurance Research Database. A control cohort without AR, which was matched for age, comorbidities and medications, was selected for comparison. The two cohorts were followed up until 31 December 2009 and observed for occurrence of ED by registry of ED diagnosis in the database.

Results: Of the 128 118 sampled male patients (64 059 AR patients vs 64 059 matched controls), 1455 (1.16%) experienced ED during a mean follow-up period of 5.82 years, including 844 (1.32% of the AR patients) from the AR cohort and 611 (0.95%) from the controls. Kaplan–Meier analysis revealed a tendency of AR patients to develop ED (log-rank test, $P < 0.001$). After adjusting confounder variables by Cox regression, subjects with AR experienced a 1.37-fold (95% CI, 1.24–1.52; $P < 0.001$) increase in incident ED. The risk of ED was higher in cases with more frequent clinical visits for AR and in cases needing medication more than 4 weeks.

Conclusions: Patients with AR appeared to be at higher risk of future ED, possibly in a severity-dependent manner.

Abbreviations

AR, allergic rhinitis; ED, erectile dysfunction; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IgE, immunoglobulin E; NHRI, National Health Research Institutes; NHIRD, National Health Insurance Research Database; ACE, angiotensin-converting enzyme; LHID2000, Longitudinal Health Insurance Database 2000; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Chronic inflammatory airway diseases, most notably chronic obstructive pulmonary disease (COPD) and asthma, have been reported to be associated with erectile dysfunction (ED) (1, 2). Allergic rhinitis (AR) is also a chronic airway inflammatory disorder, primarily involving the nose. A growing body of evidence has shown that AR is not merely a local disease, but the inflammation it produces may also propagate systemically (3, 4). Additionally, inflammatory mediators and cells involved in AR, such as leukotrienes (5), immunoglobulin E (IgE) (6) and mast cells (7), have been reported to be

implicated in the process of atherosclerosis, which is relevant to the occurrence of ED (8).

To our knowledge, only two studies, based on subjectively reported questionnaires, had investigated sexual activities of AR patients, highlighting their impaired quality of life. However, these studies were criticized for their small sample size, cross-sectional design, lack of appropriate control and lack of information regarding comorbidities and medication, thereby dampening their power to document the relationship between AR and ED (9, 10). We hypothesized AR may have a role in ED development and hence conducted this nationwide population-based study to explore their relationship.

Materials and methods

Database

The National Health Insurance is a mandatory universal health insurance program, offering comprehensive medical care coverage to all Taiwanese residents since 1995. The National Health Research Institutes (NHRI) in Miaoli (Taiwan) is in charge of the entire insurance claims database, namely the National Health Insurance Research Database (NHIRD), which consists of healthcare data from >97% of the entire Taiwan population. This study used a publicly released cohort data set, the Longitudinal Health Insurance Database 2000 (LHID2000), comprised of approximately 1 000 000 randomly sampled people who were alive during 2000 and collected all the records of these individuals from 1995 onwards. The released database has been confirmed by NHRI to be representative of the Taiwanese population and also one of the largest population-based databases in the world (11). In this cohort data set, each patient's original identifiable information has been encrypted by NHRI in a consistent manner, allowing protection of patients' privacy and linkage of claims belonging to the same patient within this database. This study was approved by the institutional review board of Taipei Veterans General Hospital (VGHIRB No. 2012-01-007AC).

Study sample and control

The study is a retrospective matched controlled cohort study. From LHID2000, we identified male patients of age 18–55 years who were freshly diagnosed with AR [*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 477, 477.0, 477.1, 477.8, 477.9] during 1 January 2000 to 31 December 2008 as the study cohort (AR cohort). Subjects who have past history of AR before 2000 were excluded. The enrolled date was defined as the date on which AR was initially diagnosed.

An age-, comorbidity- and medication-matched control group was selected from those patients without AR in the database. In both groups, subjects with pre-existing ED (ICD-9-CM codes 302.72, 607.84) before enrollment, or patients with spinal cord injury (344.1) or cancer (140.0–208.xx) throughout the whole course of follow-up were excluded (2, 12).

Variables

Risk factors associated with the development of ED were assessed and matched between the AR groups and controls, including common comorbidities and medications (2, 12–14). The comorbidities to be matched included pre-existing (upon enrollment) hypertension (ICD-9-CM codes 401.xx – 405.xx), diabetes mellitus (250.xx), coronary artery disease (410.xx – 414.xx), arrhythmia (427.xx, 785.0, 785.1), asthma (493.xx), COPD (491.xx, 494.xx, 492.xx, 496.xx), chronic kidney disease (580.xx – 587.xx), ischemic stroke (433.xx – 434.xx, 436, 437.1) and hyperlipidemia (272.0, 272.1, 272.2, 272.4).

Enrollees' drug history was retrieved upon enrollment, including angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers and statins (12). The number of clinical visits to an urologist, which may increase the chance for ED to be diagnosed, was also calculated for further adjustment (2).

Matching

Selection of controls was performed with frequency matching for each individual's age, gender, comorbidities and medication, which was achieved by a computer program written with the Perl programming language (version 5.12.2; Perl Foundation, Walnut, CA, USA). Matching for the age was allowed for a tolerance range (± 1 year). The time difference between enrollment of AR cases and controls was limited to <1 year. For the controls, the start of follow-up is defined as the first date of clinical visit to a medical facility for a given year.

Main outcome measures

The endpoint of the study was defined as occurrence of ED (ICD-9-CM codes 302.72, 607.84) (2). For every AR patient, the number of clinical visits for AR in the first year was calculated as a presumed surrogate of AR severity and further classified into three groups (<6, 6–11 and ≥ 12 visits/year). Duration of medication for AR, including antihistamine and steroids, was also dichotomized into two groups (≥ 4 weeks and <4 weeks), which may imply the duration of AR symptoms as well (15, 16).

All enrollees were followed from the enrolled date until the first diagnosis of ED or censored on the date of death, withdrawal from the insurance or until 31 December 2009 if there was absence of ED.

Statistical analysis

Extraction and computation of data were performed using the Perl programming language (version 5.12.2). Microsoft SQL Server 2005 (Microsoft Corp., Redmond, WA, USA) was used for data linkage, processing and sampling. Statistical analysis was performed utilizing SPSS software (Version 17.0, SPSS, Inc., Chicago, IL, USA). All data were expressed as mean $\pm$ standard deviation (SD) or percentage unless otherwise stated. Comparisons between two groups were

determined by independent Student's *t*-test or Pearson's chi-squared test as appropriate. The number of clinical visits for a urologist between the two groups was compared by Mann–Whitney *U*-test because it was not normally distributed. Tolerance and variance inflation factor were used to assess collinearity.

Survival analysis was conducted using the Kaplan–Meier method, with the significance based on the log-rank test. A Cox proportional hazard model was used for multivariate adjustment if the proportional hazards assumption was satisfied. Statistical significance was inferred at a two-sided *P* value of < 0.05.

Results

Of 64 059 freshly diagnosed male AR patients (mean age, 34.25 ± 10.62 years) were identified from the 999 953 sampling cohort data sets between 1 January 2000 and 31 December 2008, whereas another 64 059 male subjects without AR (mean age, 34.25 ± 10.62 years) served as the control group. The two cohorts had similar features (Table 1), except that the AR group had more frequent clinical visits to an urologist than did the control group (1.12 *vs* 0.75, *P* < 0.001). Most enrollees in both groups (94.32% in AR cohort and 96.52% in the control group) remained active and were followed through the end of study (Fig. 1).

During 5.82 ± 2.55 years' follow-up, there were more ED events among AR patients as compared with the control group [844 (1.32%) *vs* 611 (0.95%)]. AR patients had a significantly higher hazard for future ED events than those without AR (log-rank test, *P* < 0.001, Fig. 2).

The proportional hazards assumption was tested and not violated, allowing a multivariate analysis to proceed with the Cox model. For each variable for adjustment in this model, no evident collinearity was noted (variance inflation factor: 1.002–1.397, tolerance: 0.716–0.998).

After multivariate adjustment, AR (HR: 1.37, 95% CI: 1.24–1.52, *P* < 0.001, Table 2) was independently associated with ED development. Furthermore, the adjusted risk of ED increased significantly with numbers of clinical visits for AR (HR of clinical visits with ≥ 12 , 6–11 and <6 times/year, as compared with control, 2.41, 1.63 and 1.36, respectively, Table 3). The risk was also higher in cases needing medication longer than 4 weeks (HR of AR patients with medication for ≥ 4 weeks and for <4 weeks, as compared with control, 1.56 and 1.33, respectively, Table 3). If only AR patients considered, HR of AR patients with medication ≥ 4 weeks *vs* <4 weeks was 1.18 [95% CI: 1.01–1.39], *P* = 0.044 (not shown). The subgroup analysis was also presented in Fig. 3. HRs of AR were all statistically significant higher in their counterparts devoid of a given comorbidity (not shown), suggesting the independent role of AR on ED development.

Discussion

To our knowledge, this study is the first large-scale study to identify AR as an independent risk factor for ED. We also have demonstrated the 'exposure–response relationship', in

Table 1 Demographic data for patients with AR and control (*n* = 128118)

Characteristics	AR	Control	<i>P</i> value
<i>n</i>	64059	64059	
Male	100%	100%	
Age	34.25 ± 10.62	34.25 ± 10.62	1
Follow-up time (years)	5.79 ± 2.55	5.84 ± 2.56	0.001 [†]
Comorbidities			
Hypertension (%)	6582 (10.27)	6586 (10.28)	0.98
Diabetes mellitus (%)	3431 (5.36)	3436 (5.36)	0.96
Coronary artery disease (%)	3329 (5.20)	3329 (5.20)	1
Arrhythmia (%)	4241 (6.62)	4227 (6.60)	0.88
COPD (%)	7724 (12.06)	7676 (11.98)	0.69
Asthma (%)	6765 (10.56)	6710 (10.47)	0.62
Chronic kidney disease (%)	2496 (3.90)	2480 (3.87)	0.83
Ischemic stroke (%)	581 (0.91)	581 (0.91)	1
Hyperlipidemia (%)	6961 (10.87)	6958 (10.86)	0.99
Medication			
ACE inhibitor (%)	1532 (2.39)	1507 (2.35)	0.65
Beta blocker (%)	4182 (6.53)	4157 (6.49)	0.78
Statins (%)	2160 (3.37)	2125 (3.32)	0.59
Number of visits to an urologist	1.12 (0–257) [§]	0.75 (0–217) [§]	< 0.001 [‡]
Development of ED during follow-up	844 (1.32)	611 (0.95)	< 0.001 [*]

AR, allergic rhinitis; ED, erectile dysfunction; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.

Data are given as mean $\pm$ SD or *n* (percentage). *P* values are determined by Pearson's chi-square test unless mentioned otherwise.

*Kaplan–Meier analysis.

[†]Independent *t*-test.

[‡]Mann–Whitney *U*-test.

[§]Range.

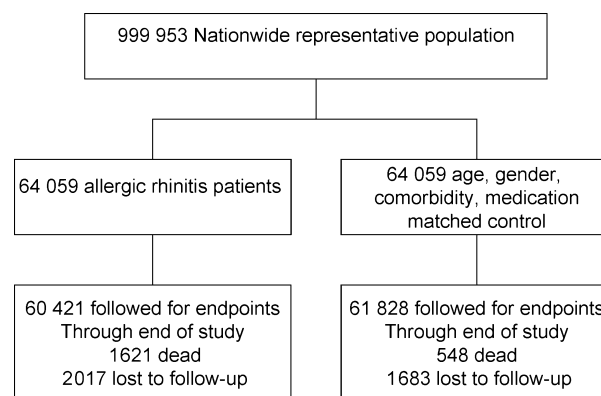


Figure 1 A flow diagram illustrating the follow-up process of AR patients and matched controls.

that the patients with more frequent clinical visits for AR or longer duration of AR medication conferred a higher risk of ED.

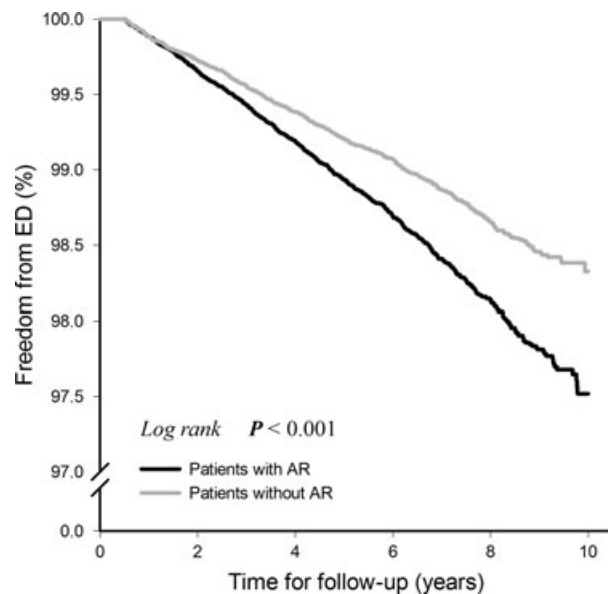


Figure 2 Kaplan-Meier plot of ED-free probabilities in patients with and without AR. There was a statistically significant difference between the two curves (log-rank test, $P < 0.001$).

Table 2 Determinants of ED by cox proportional hazards regression analysis*

Characteristics	HR	95% CI for HR	P value
AR	1.37	1.24–1.52	< 0.001
Age	1.04	1.04–1.05	< 0.001
Hypertension	0.85	0.72–1.01	0.068
Diabetes mellitus	1.48	1.24–1.77	< 0.001
Coronary artery disease	1.14	0.94–1.38	0.19
Arrhythmia	1.23	1.02–1.48	0.029
COPD	1.31	1.15–1.50	< 0.001
Asthma	1.23	1.06–1.43	0.007
Chronic kidney disease	1.80	1.50–2.18	< 0.001
Ischemic stroke	1.34	0.92–1.94	0.13
Hyperlipidemia	0.99	0.84–1.16	0.87
ACE inhibitors	1.25	0.99–1.56	0.058
Beta blockers	1.34	1.13–1.58	0.001
Statins	1.14	0.94–1.40	0.19
Number of visits to an urologist	1.02	1.01–1.02	< 0.001

AR, allergic rhinitis; ED, erectile dysfunction; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.

Bold values indicate those variables with $P < 0.05$.

*The Cox model included age, comorbidities, medication and the number of clinical visits to an urologist for adjustment.

There were few studies addressing the relationship between AR and sexual dysfunction. In 2005, Cengiz Kirmaz et al. (9) reported, based on the data collected from the self-administered questionnaires, patients with allergic rhinoconjunctivitis had impaired sexual function, which improved after treatment. Despite Kirmaz et al. having utilized the International Index of Erectile Function containing some specific questions to

Table 3 Association of the risk of developing ED with the number of clinical visits for AR and duration of medication for AR

Clinical visits for AR	HR*	95% CI	P value
Control (0 visit/year)	Referent		
<6 visits/year	1.36	1.22–1.51	< 0.001
<12 & ≥ 6 visits/year	1.63	1.20–2.22	0.002
≥ 12 visits/year	2.41	1.25–4.65	0.009
Duration of medication for AR			
Control	Referent		
<4 weeks	1.33	1.19–1.48	< 0.001
≥ 4 weeks	1.56	1.33–1.84	< 0.001

AR, allergic rhinitis; ED, erectile dysfunction; HR, hazard ratio; CI, confidence interval.

*The HRs were adjusted for age, comorbidities, medication and the number of clinical visits to an urologist.

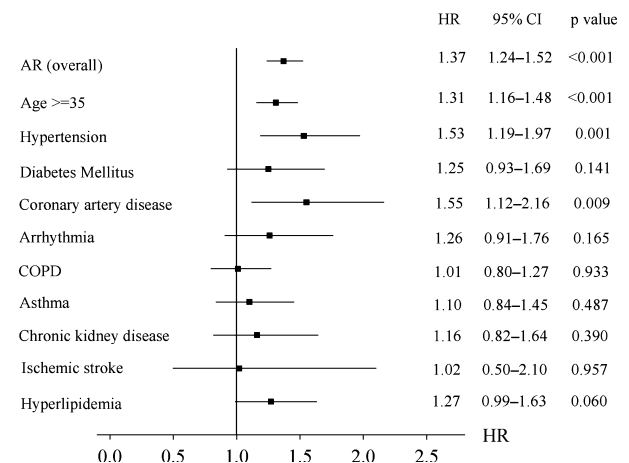


Figure 3 HRs of AR for risk of incident ED in subgroup analysis. HRs were adjusted for age, comorbidities, medication and the number of clinical visits to an urologist.

evaluate erectile function, their study population consisted of only 16 and 20 men in the study and the control group, respectively. In 2009, another study, by Michael S. Benninger, integrated the results of questionnaires obtaining from several cohorts and analyzed the answers to one of the questions in the questionnaires, 'My sexual activity is affected by my problem?' He concluded AR had unfavourable impact on sexual function (10). The two studies did suggest AR may be associated with impaired sexual function and quality of life, but the relationship between AR and ED was still not fully elucidated.

Systemic propagation of inflammation in patients with chronic airway diseases has been extensively studied (17). COPD, the most notable one, has been reported to be linked with development of cardiovascular complications, including ED (1, 18). Furthermore, several studies, although with inconsistent findings, described association between asthma and cardiovascular disease, including coronary/carotid atherosclerosis and stroke (19–21). Our previous work also demonstrated asthma confers a higher risk of ED (2).

Accumulative evidence suggested low-grade systemic inflammation accompanying these airway diseases underlies the linkage to the development of cardiovascular consequences as well as ED (18, 22, 23).

Inasmuch as AR is also an inflammatory airway disease, albeit thought to be milder in severity as compared with COPD or asthma, it probably exerts systemic inflammatory effect in a similar fashion, thereby contributing to cardiovascular or cerebrovascular consequences (3, 4). However, no studies reporting elevated systemic inflammation markers in AR patients are currently available. In addition, little research has addressed the relationship between AR and cardiovascular diseases. Matheson et al. (24) analyzed a cohort of 9272 middle-aged and elderly and identified AR as a risk factor for incident stroke. Apart from this, the link between AR and other cardiovascular diseases awaits exploration.

ED is associated with the presence and extent of asymptomatic atherosclerosis and may serve as a harbinger of cardiovascular disease (25, 26). If systemic inflammation does exist in patients with AR, although to a lesser extent than in patients with asthma or COPD, ED may be a better target to evaluate its impact on vasculature compared with other overt cardiovascular diseases.

In the setting of acute AR attacks, a blocked or runny nose is possible to decrease the libido of the affected individuals, thereby promoting occurrence of ED (16). However, over the long term, whether AR has a role in ED development remained unexplored. The link between allergic diseases and cardiovascular consequences could be explained by the emerging role of leukotrienes and IgE in the pathogenesis of atherosclerosis. Leukotrienes are common inflammatory mediators in AR and asthma, which can be released by a variety of inflammatory cells involved in the allergic response, such as mast cells and eosinophils. A growing body of evidence has shown leukotrienes may have a role in the pathogenesis of cardiovascular diseases and may promote atherosclerosis, via increased leukocyte chemotaxis, vascular inflammation and enhanced permeability, and subsequent tissue/matrix degeneration (27). IgE, another principal mediator in AR, has also been implicated in the process of atherosclerosis. Several studies mentioned the association of serum IgE level with severity of cardiovascular disease. Recently, Jing Wang et al. (6) confirmed the direct role of IgE in atherogenesis by demonstrating the presence of IgE in human atherosclerotic lesions and its necessity for inducing inflammatory molecule expression and apoptosis of macrophages in murine atherosclerotic plaques. The above finding implies AR is possibly related to atherosclerosis and, hence, ED development.

Research investigating nasobronchial cross-talk also provides support for systemic propagation of nasal inflammation in AR patients. The study by Braunstahl et al. evaluated the number of eosinophils and expression of adhesion molecules in nasal and bronchial epithelium after nasal allergen provocation. Their results showed 24 h after nasal allergen provocation, more influx of eosinophils and increased expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin were seen in both nasal and bronchial tissue of patients with AR, compared with the baseline and with the controls (28). Cellular

adhesion molecules facilitate tethering of circulating leukocyte and other blood cells to activated vascular endothelium at sites of inflammation, which is also implicated in the pathogenesis of atherosclerosis (29). Expression of adhesion molecules can be enhanced by proinflammatory cytokines, for example, tumor necrosis factor- α (TNF- α) released by mast cells during the allergic response (30). Elevated serum levels of ICAM-1 and VCAM-1 in perennial AR patients have also been reported (31, 32). Evidence from prospective studies has identified the plasma levels of these molecules as a useful marker in predicting further cardiovascular events (33, 34). Interestingly, similar elevation of circulating adhesion molecules was also observed in ED patients without cardiovascular risk factors, further strengthening the potential link of AR and ED (35). More research is needed to clarify the role of adhesion molecules in the relationship between AR and ED.

In addition to AR, we also identified several factors related to ED. However, it did not mean other vascular pathologies nonsignificant in the multivariate analysis (ex. coronary artery disease) played no role in ED development. Our conclusion may be confined to the AR population, which is younger (aged 34 years on average in this study) and with fewer comorbidities. For such population, patients with cardiovascular diseases accounted for a small fraction and the diseases tend to be milder in severity (even asymptomatic) or to last for a relatively shorter period, hence not favouring a significant effect to document. Despite this, emergence of ED may precede the development of overt cardiovascular diseases (25, 26).

One particular strength of our study is its nationwide, population-based study design, which could trace all cases of newly diagnosed AR and ED in Taiwan during the study period, because all rhinologic and urological practice were covered in our insurance system. Additionally, the large sample size of this study afforded substantial statistical power for detecting real, even subtle, differences between the two cohorts.

Nevertheless, this study has several limitations. Diagnoses of AR and ED that rely on administrative claims data registered by physicians or hospitals may be less accurate than diagnoses made in a clinical, prospective setting. Secondly, some personal information, including body mass index and smoking, was not available in the administrative data, which might interact with ED development. Finally, the external validity of our findings may be a concern because our study subjects are of Chinese ethnicity. Generalizability of our results to other non-Asian ethnic group needs to be further verified.

In conclusion, AR may be a potential risk factor for ED, and the risk probably increases in accordance with AR severity.

Author contributions

Kun-Ta Chou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Vincent Yi-Fong Su, Chia-Jen Liu and Kun-Ta Chou contributed to the study concept and design. Chia-Jen Liu was involved in the acquisition of data. Chia-Jen Liu, Kun-Ta Chou and Vincent Yi-Fong Su performed the analysis and interpretation of data. Kun-Ta Chou

and Vincent Yi-Fong Su drafted the manuscript. Ming-Ying Lan, Yuh-Min Chen, Kang-Cheng Su, Chia-Jen Liu, Yu-Chin Lee and Tzeng-Ji Chen carried out critical revision of the manuscript for important intellectual content. Chia-Jen Liu, Kun-Ta Chou and Vincent Yi-Fong Su performed the statistical analysis. Yu-Chin Lee, Tzeng-Ji Chen provided administrative, technical or material support. Yu-Chin Lee supervised the work.

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Conflict of interest

All the authors declare that there is no potential conflict of interest.

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