



Association between chronic idiopathic urticaria and hypertension A population-based retrospective cohort study

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ARTICLE INFO

Article history:

Received for publication December 12, 2015.

Received in revised form March 28, 2016.

Accepted for publication April 5, 2016.

ABSTRACT

Background: Chronic idiopathic urticaria (CIU) is defined as urticaria that is not caused by external triggers. The pathogenesis of CIU remains unknown. A previous study investigated whether hypertension is associated with extended duration of CIU.

Objective: To investigate the possible association between CIU and hypertension.

Methods: We performed a population-based retrospective cohort study of 2,460 patients with CIU and 9,840 age-, sex-, and index year-matched comparison patients, using the National Health Insurance of Taiwan database. The median follow-up periods were 7.13 years for the CIU cohort and 7.20 years for the non-CIU cohort. The distributions by sex and age were similar for both cohorts.

Results: The CIU cohort had a 1.37-fold (95% CI, 1.22–1.53) greater risk of developing subsequent hypertension than the non-CIU cohort after adjusting for sex, age, comorbidities, and nonsedating antihistamine use.

Conclusion: This nationwide retrospective cohort study found that CIU is associated with a higher future risk of hypertension after adjusting for sex, age, comorbidities, and nonsedating antihistamine use. The detailed pathophysiologic mechanisms require further clarification in prospective studies.

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Introduction

Chronic urticaria, as opposed to acute urticaria, is defined by the presence of hives, usually occurring daily for 6 weeks or longer. Chronic idiopathic urticaria (CIU) is defined as urticaria that is not caused by external triggers, such as a physical stimuli (pressure, heat, and cold). The cause is unknown, and the condition lasts for at least 6 weeks.¹ Recently, the term *chronic spontaneous urticaria*

(CSU) has become more widely used than CIU to emphasize an endogenous cause rather than an exogenous cause and its non-inducible nature as opposed to that of an inducible condition.²

The pathogenesis of CIU and CSU remains unknown, but autoimmune abnormalities, disorders of histamine-releasing factors, and cellular defects have all been theorized to potentially play a role.³ In addition, the prognosis is unpredictable, and treatment remains challenging; up to 40% of patients with urticaria persisting beyond 6 months will continue to have symptoms 10 years later.¹

A previous study¹ investigated the effect of various clinical parameters on the duration of urticaria and reported that hypertension was associated with an extended duration of CIU. This observation suggested a new approach to antihistamine-refractory CIU treatment: the treatment and optimal control of hypertension.¹ The aim of the present study was to evaluate the incidence of hypertension in patients with CIU, using the National Health Insurance (NHI) of Taiwan database. We hope our findings will help elucidate the mechanisms of CIU and allow more efficacious treatments in the future.

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Disclosures: Authors have nothing to disclose.

Funding Sources: This study was supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM10501010037), National Research Program for Biopharmaceuticals Stroke Clinical Trial Consortium (MOST 104-2325-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

<http://dx.doi.org/10.1016/j.anai.2016.04.001>

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Methods

Data Source

The National Health Insurance Research Database (NHIRD), established in 1996, comprises data derived from the reimbursement claims of beneficiaries of the NHI program covering more than 99% of the total population of Taiwan. The study cohort was created using the Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD. The LHID 2000 comprises a random sample of longitudinally linked data available from 1996 through 2011 for 1 million individuals from the NHIRD. Disease diagnoses are coded using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. This study was approved by the institutional review board of China Medical University in central Taiwan (CMUH104-REC2-115).

Study Population

This study consisted of 2 cohort groups. The population of 1 cohort group had been newly diagnosed as having idiopathic urticarial disease and had at least 2 claims for the ICD-9-CM diagnosis code 708.1 from 2000 to 2006. All patients were older than 20 years. The index date for the cohort group was defined as the date of the initial outpatient or inpatient diagnosis of idiopathic urticarial disease. Individuals in the control group were randomly selected from the same database. Each patient in the newly diagnosed idiopathic urticarial disease cohort was pair-matched with 4 same-sex individuals within 5 years of the patient's age from the same index year in the NHRI database. For the control group, the index year was randomly assigned from January 2000 to December 2006 according to the index date distribution of nonidiopathic urticarial disease. We excluded those younger than 20 years and those who had been diagnosed as having hypertension before the diagnosis of idiopathic urticarial disease.

Study Outcome and Comorbidity

The primary outcome was a new diagnosis of hypertension (ICD-9-CM code 401) defined as the first outpatients or inpatient visit index date during the follow-up period. The follow-up period began with the index date and ended at the time of a new diagnosis of hypertension, withdrawal from insurance, or the end of the study on December 31, 2011. Patients with claim records reporting a history of diabetes mellitus (ICD-9-CM code 250 or A-code A181) and hyperlipidemia (ICD-9-CM code 272.0–272.4) identified at index date were considered to have comorbidities. We defined antiurticaria drug use as more than 42 cumulative days of treatment with 1 of the following drugs: cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.

Statistical Analysis

Descriptive statistics were used to examine the baseline characteristics of the study cohort groups. We used the Pearson χ^2 test for categorical variables and the *t* test for continuous variables. We estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) for each variable using the Cox proportional hazards model. The multivariate model was adjusted for sociodemographic factors, comorbidity, and antiurticaria drug use. We plotted the Kaplan-Meier curves to compare the cumulative incidence of hypertensive disease between both groups during the study period and used the log rank test to examine the differences between both groups. All statistical analyses were performed with SAS statistical analysis software, version 9.4 (SAS Institute Inc, Cary, North Carolina), and the significance level was set at .05.

Table 1

Characteristics of Participants With and Without Chronic Idiopathic Urticaria

Variable	Chronic idiopathic urticaria ^a		P value
	No (n = 9,840)	Yes (n = 2,460)	
Sex			.99 ^b
Women	6,360 (64.63)	1,590 (64.63)	
Men	3,480 (35.37)	870 (35.37)	
Age, y			.99 ^b
20–39	5,920 (60.16)	1,480 (60.16)	
40–64	3,432 (34.88)	858 (34.88)	
≥65	488 (4.96)	122 (4.96)	
Mean (SD)	38.23 (13.77)	38.38 (13.62)	.62 ^c
Comorbidity			
Diabetes mellitus	424 (4.31)	133 (5.41)	.02 ^b
Hyperlipidemia	448 (4.55)	169 (6.87)	<.001 ^b
Drug use (>42 days cumulative use)			
Cetirizine	704 (7.15)	596 (24.23)	<.001 ^b
Desloratadine	98 (1)	62 (2.52)	<.001 ^b
Fexofenadine	212 (2.15)	173 (7.03)	<.001 ^b
Levocetirizine	136 (1.38)	107 (4.35)	<.001 ^b
loratadine	713 (7.25)	497 (20.2)	<.001 ^b
Follow-up period, mean (median)	7.04 (7.20)	6.97 (7.13)	
Outpatient visits, mean (SD) (follow-up 6 years after index date)	73.84 (67.17)	113 (81.16)	<.001 ^c

^aData are presented as number (percentage) unless otherwise indicated.

^b χ^2 test.

^cTwo-sample *t* test.

Results

Table 1 shows the demographic results for our study population. After excluding ineligible people, the study included 2,460 patients with CIU and 9,840 age-, sex-, and index year–matched comparison patients. The mean (SD) age of the CIU cohort was 38.38 (13.62) years and that of the comparison cohort was 38.23 (13.77) years. The median follow-up period was 7.13 years for the CIU cohort and 7.20 years for the non-CIU cohort. The distributions by sex and age were similar for both cohorts. Compared with the non-CIU group, the CIU group had a higher proportion of diabetes mellitus, hyperlipidemia, and antiurticaria drug use.

Table 2 gives the univariable and multivariable Cox proportional hazards models in the CIU cohort vs the non-CIU cohort. The significant crude HRs for hypertension in the Cox proportional hazards model were 1.23 (95% CI, 1.1–1.38) for CIU, 0.63 (95% CI, 0.57–0.69) for female, 5.97 (95% CI, 5.29–6.73) for age of 40 to 64 years, 15.19 (95% CI, 12.99–17.77) for age older than 65 years, 0.26 (95% CI, 0.23–0.3) for diabetes mellitus, 0.23 (95% CI, 0.23–0.3) for hyperlipidemia, 0.6 (95% CI, 0.5–0.72) for use of cetirizine, 0.46 (95% CI, 0.26–0.83) for use of desloratadine, 0.64 (95% CI, 0.46–0.9) for use of fexofenadine, 0.45 (95% CI, 0.28–0.74) for use of levocetirizine, and 0.67 (95% CI, 0.56–0.8) for use of loratadine. With multivariate Cox proportional hazards model analysis using 9 control factors (female, age, diabetes mellitus, hyperlipidemia, and use of cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine), CIU retained a high risk for hypertension (HR, 1.37; 95% CI, 1.22–1.53). The Kaplan-Meier analysis revealed a higher cumulative incidence of developing hypertension in the CIU cohort compared with the non-CIU (Fig 1).

In the subgroup analysis, we found that female patients, patients aged 20 to 39 years, patients aged 40 to 59 years, patients without diabetes mellitus, and patients with or without hyperlipidemia had higher adjusted HRs for developing hypertension (Table 3).

Discussion

Previous studies have found that hypertension is associated with an extended duration of CIU, suggesting a new approach to the

Table 2

Cox Proportional Hazards Model With HRs and 95CIs of Hypertension Associated With Chronic Idiopathic Urticaria

Variable	Hypertension, No. (n = 1,691)	Crude		Adjusted ^a	
		HR (95%CI)	P value	HR (95%CI)	P value ^b
Chronic idiopathic urticaria					
No	1296	1 [Reference]		1 [Reference]	
Yes	395	1.23 (1.1–1.38)	<.001	1.37 (1.22–1.53)	<.001
Sex					
Women	926	0.63 (0.57–0.69)	<.001	0.82 (0.74–0.9)	<.001
Men	765	1 [Reference]		1 [Reference]	
Age, y					
20–39	349	1 [Reference]		1 [Reference]	
40–64	1056	5.97 (5.29–6.73)	<.001	5.35 (4.73–6.05)	<.001
≥65	286	15.19 (12.99–17.77)	<.001	12.42 (10.56–14.61)	<.001
Comorbidity					
Diabetes mellitus					
No	1477	1 [Reference]		1 [Reference]	
Yes	214	0.26 (0.22–0.3)	<.001	1.75 (1.49–2.04)	<.001
Hyperlipidemia					
No	1458	1 [Reference]		1 [Reference]	
Yes	233	0.26 (0.23–0.3)	<.001	1.77 (1.52–2.05)	<.001
Drug use (>42 days cumulative use)					
Cetirizine					
No	1570	1 [Reference]		1 [Reference]	
Yes	121	0.6 (0.5–0.72)	<.001	0.65 (0.53–0.8)	<.001
Desloratadine					
No	1680	1 [Reference]		1 [Reference]	
Yes	11	0.46 (0.26–0.83)	.01	0.71 (0.38–1.32)	.28
Fexofenadine					
No	1655	1 [Reference]		1 [Reference]	
Yes	36	0.64 (0.46–0.9)	.009	0.69 (0.49–0.96)	.03
Levocetirizine					
No	1675	1 [Reference]		1 [Reference]	
Yes	16	0.45 (0.28–0.74)	.002	0.65 (0.39–1.1)	.12
Loratadine					
No	1564	1 [Reference]		1 [Reference]	
Yes	127	0.67 (0.56–0.8)	<.001	0.73 (0.6–0.89)	.002

Abbreviations: HR, hazard ratio; CI, confidence interval.

^aMutually adjusted for chronic idiopathic urticaria, age, sex, diabetes mellitus, hyperlipidemia, and drug use in Cox proportional hazards regression.^bP values < .05 were significant.

treatment of antihistamine-refractory CIU: the treatment and optimal control of hypertension. This study found that the CIU cohort had a 1.37-fold (95% CI, 1.22–1.53) (Table 3) greater risk of developing subsequent hypertension than the non-CIU cohort after adjusting for sex, age, comorbidities, and antiurticaria drug use.

This study found an association between hypertension and CIU, an association possibly attributable to alterations in the blood coagulation and fibrinolysis pathways. Recent studies have found that systemic hypertension is commonly associated with a pro-coagulant state.⁴ In addition, other studies have suggested that the coagulation cascade pathway may contribute to the pathogenesis of CIU, especially in antihistamine-refractory cases. The successful treatment of CIU with the anticoagulant warfarin was reported in a small, double-blind, placebo-controlled, crossover study of patients with CIU refractory to antihistamines. The findings of that study are consistent with other studies reporting that the extrinsic pathway of the clotting cascade is activated in CIU.^{5,6} A recent study by Takahagi et al⁷ also found that plasma fibrin/fibrinogen degradation product (D-dimer) levels may be useful in the assessment of CIU disease activity. Asero et al⁸ also observed that severe CIU is associated with elevated plasma D-dimer levels.

The link between CIU and hypertension may also be related to inflammation. Several studies have suggested that inflammation markers, such as pentraxin-3 and serum C-reactive protein, may be useful for the assessment of CIU disease activity.^{7,9} In addition, a number of studies have found an association between inflammation markers and hypertension. A study by Hage¹⁰ suggested that C-reactive protein is a strong, precise, accurate, and independent marker of cardiovascular disease risk and is also associated with hypertension and markers of arterial stiffness and end-organ

damage in hypertensive patients. In addition, a study by Yano et al¹¹ indicated that pentraxin-3 is a useful inflammatory biomarker for predicting cognitive impairment in elderly hypertensive patients.

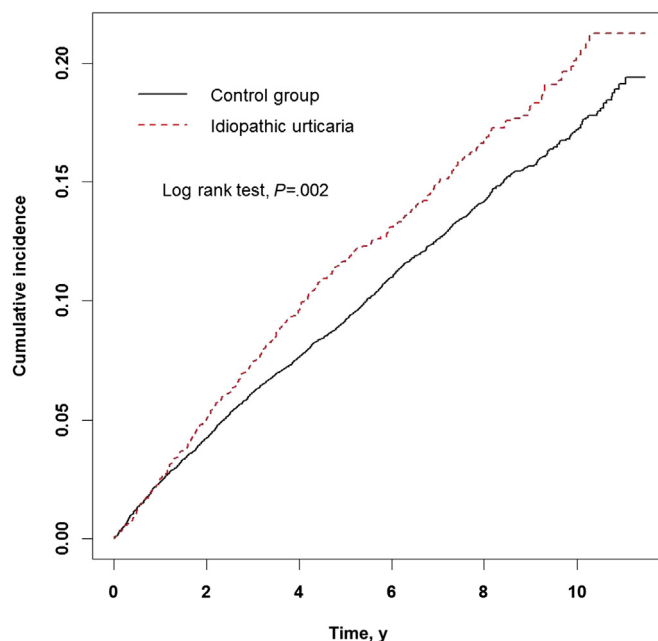


Figure 1. The estimated cumulative incidence of hypertension between the chronic idiopathic urticaria cohort and the control cohort using Kaplan-Meier analysis.

Table 3
IRs, HRs, and 95% CIs of Hypertension Associated With Chronic Idiopathic Urticaria

Variable	Chronic idiopathic urticaria						Crude HR (95% CI)	Adjusted HR ^a (95% CI)
	No (n = 9,840)			Yes (n = 2,460)				
	Event	Person-years	IR	Event	Person-years	IR		
Total	1296	69,275	18.71	395	17154	23.03	1.23 (1.10–1.38) ^b	1.37 (1.22–1.53) ^b
Sex								
Women	732	45,501	16.09	194	11361	17.08	1.06 (0.91–1.24)	1.21 (1.03–1.43) ^c
Men	564	23,774	23.72	201	5793	34.70	1.46 (1.25–1.72) ^b	1.55 (1.31–1.83) ^b
Age, y								
20–39	261	44,283	5.89	88	11068	7.95	1.35 (1.06–1.72) ^c	1.50 (1.17–1.92) ^d
40–59	809	22,596	35.80	247	5491	44.98	1.26 (1.09–1.45) ^d	1.36 (1.17–1.57) ^b
≥60	226	2,396	94.31	60	595	100.91	1.06 (0.80–1.41)	1.19 (0.89–1.61)
Comorbidity								
Diabetes mellitus								
No	1129	66,933	16.87	348	16414	21.20	1.26 (1.11–1.42) ^b	1.41 (1.24–1.59) ^b
Yes	167	2,343	71.29	47	740	63.54	0.89 (0.64–1.23)	1.05 (0.75–1.46)
Hyperlipidemia								
No	1,132	66,727	16.96	326	16242	20.07	1.18 (1.05–1.34) ^d	1.35 (1.19–1.53) ^b
Yes	164	2,548	64.36	69	912	75.62	1.18 (0.89–1.56)	1.45 (1.09–1.93) ^c

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 1,000 person-years.

^aAdjusted for chronic idiopathic urticaria, age, sex, comorbidity, and drug use in Cox proportional hazards regression.

^b $P < .001$.

^c $P < .05$.

^d $P < .01$.

Research has revealed an association between CIU and autoimmunity.^{2,12,13} A previous case report described the successful treatment of CIU with intravenous cyclophosphamide.¹⁴ In addition, several studies have reported that oral cyclosporine is effective in treating CIU patients, and the results provide further evidence to support the CIU autoimmune pathogenetic hypothesis.^{15–19} In a large study, the prevalence of autoimmune disorders in nearly 13,000 patients with CIU was compared with more than 10,000 control patients. The investigators found that autoimmune disorders, such as thyroid disorders, celiac disease, Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes mellitus, were more prevalent in patients with CIU than in controls.²⁰ Therefore, autoimmunity plays an important role in CIU. Recently, a number of studies have suggested that self-antigens and the subsequent activation of the adaptive immune system promote the development of hypertension.²¹ Other studies have found that hypertension is prevalent in some of the most common autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus.^{21–23} Studies have also revealed the importance of T-cell subsets and specific inflammatory cytokines in both human and experimental hypertension.^{24–27} Finally, an increasing body of evidence exists that claims that the loss of immune tolerance and the production of autoantibodies associated with autoimmunity can have a pathogenic role in the development of hypertension.²¹ Therefore, CIU and hypertension may be linked through autoimmunity.

A strength of our study is the use of population-based data that are highly representative of the general population. However, our study has some limitations. The evidence derived from a retrospective cohort study is generally lower in statistical quality than that derived from randomized trials because of potential biases related to adjustments for confounding variables. Despite our meticulous study design and control measures for confounding factors, biases resulting from unknown confounding variables may have affected our results. For example, adding all the patients with CIU who used antihistamines for more than 42 days, approximately 40% of patients with CIU did not use any nonsedating antihistamine drugs for more than 42 days during the mean follow-up of 7 years. The reason is that patients may turn to complementary and alternative medicine (traditional Chinese medicine is very popular in Taiwan) before taking nonsedating antihistamine drugs for 42 days.

However, Taiwan launched the NHI program, operated by a single payer, the government, in 1995. All insurance claims are scrutinized by medical reimbursement specialists and subject to peer review. Therefore, the data regarding the diagnoses of CIU and hypertension were reliable.

In conclusion, this nationwide retrospective cohort study found that CIU is associated with a higher future risk of hypertension after adjusting for sex, age, comorbidities, and antiurticaria drug use. In addition, the use of antihistamines appears to have a protective effect on the crude and adjusted HRs. The detailed pathophysiologic mechanisms require further clarification in prospective studies. In the future, the pathogenesis of CIU will be elucidated, and more reliable clinical tests, prognostic factors, and treatment options will become available.

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