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Original Article

The incidence of bullous pemphigoid and related clinical factors of medication and neurological disorders co-morbidity in TAIWAN

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Background: The autoimmune skin disorder, bullous pemphigoid(BP), is associated with considerable morbidity and mortality, but the epidemiological and clinical characteristics are little known. We carried out this nationwide nested case–control study to show the incidence trend, medication and neurological co-morbidities of BP. Methods: The National Health Insurance dataset (LHID2000) was used for this study. BP and neurological disorders were defined according to the ICD-9 diagnostic codes, and medications including antihypertensive, antibiotic, diuretic, NSAID, and salicylate were identified. Each case was age-(+-1 year) and sex-matched to four healthy controls. Results: The standardized BP incidence range is 1.28-3.04 per 100,000 and BP incidences in age>=70 group are 50-60 folds higher than in age<=50 group. Prescribed diuretic, salicylate, NSAID, and antihypertensive, are associated with incident BP. BP patients have high neurological comorbidities.
Conclusion: BP incidences in Taiwan are 5-30 folds higher than in the developed European countries. The associations between BP and the use of multiple drugs and neurological comorbidities shed light on future research and clinical practice of BP.

Keywords: Bullous Pemphigoid, incidence, drug use, neurological disorder, comorbidity

Introduction

The autoimmune skin disorder, bullous pemphigoid(BP), is characterized by blistering of the skin and mucous membranes[1 2]. BP is associated with the common immunobullous diseases, some morbidities, and even mortality in the United Kingdom and some other European countries[3 4].Nevertheless, the epidemiological and clinical characteristics such as multiple drugs and comorbidities require more exploration.

Studies in Malaysia, Spain, UK, and Europe, reported the BP incidences were between 2 and 43 per

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million person years[3-7]. The incidences were high in male and extremely high in the elderly, especially aged over 80 years old[8].

Neurological disorders, cerebrovascular disease, dementia, multiple sclerosis, epilepsy, and Parkinson disease[9-13], were related to BP. Taghipour et al. observed the associations of BP and four major neurologic diagnoses including cerebrovascular disease, dementia, Parkinson disease, and epilepsy. They found cerebrovascular disease and dementia significantly associated with BP, and the ORs were 6.3 folds for cerebrovascular disease and 7.9 folds for dementia[2].

The incident of BP were suggested to be related to multiple drugs[14], including furosemide[15-22], angiotensin converting enzyme inhibitors (ACEIs)[23], beta-blockers[24], penicillins[25] and anti–tumor necrosis factor agents[26].

Many reports are small sample size and hospital based, which are susceptible to selection bias. Additionally, there are rare BP reports regarding clinical characteristics in Asia. We carried out this nationwide nested case–control study in Taiwan, to show the epidemiologic and clinical characteristics of BP.

Materials and Methods

Resource of databank

This study use the Longitudinal Health Insurance Database(LHID2000) in the National Health Insurance(NHI) data bank. LHID2000 contains all the original claim data (year 1996 to year 2011) of 10000,000 individuals randomly sampled from the 2000 Registry for Beneficiaries (ID) of the NHI research dataset.NHI was implemented in 1995 in Taiwan. By 2015, 23.737 millions of Taiwanese, coverage 99.65%, were enrolled in the program to receive all forms of health care services. The NHI data bank includes comprehensive information of participants such as demographics data, time of clinical visits, diagnostic codes, prescriptions and so on. Personal, physicians', and medical care institutions' identities were scrambled in compliance with the Personal Electronic Data Protection Law.

Study sample

BP is a rare disease as its incidence 2.7 per 100000[27] in Taiwan. Dermatologists would code BP deliberately. The BP case group is composed of those with at least one BP diagnoses, ICD-9 code 694.5. We randomly selected 17425 age-(+-1 year) and sex-matched subjects (1:4) from LHID 2000 cohort. The control subjects had no diagnostic codes for BP or other bullous skin diseases (ICD-9 codes 694, 694.1–694.4, 694.6, 694.8, 694.9). The age at BP onset was based on the first record with the aforementioned code.

Four neurological diseases coexisting with BP were evaluated. Patient had the corresponding ICD-9 codes in the diagnosis fields (diagnosis made by specialists), stroke (ICD-9 codes 436, 438.9), dementia (ICD-9 code 290, 291.2, 292.82, 294.1, 294.10, 294.11, 298.9), Parkinson disease (ICD-9 code 332), and epilepsy (ICD-9 code 345).

The older people commonly use medications for hypertension, infection, analgesic (pain-killing) effect and antipyretic (fever-reducing) effect. This study explored the relation of multiple drug uses including anti-hypertensives, diuretics, antibiotics, Salicylates, and other NSAIDs(NonSteroidal Anti-Inflammatory Drug). Antihypertensive drugs included ACEI(Enalapril, Lisinopril), Beta-blockers(Nadolo), Ca-blockers(Amlodipine, Nifedipine), and Angiotensin II receptor antagonists (Losartan); Diuretics included Furosemide, and Spironolactone; Antibiotics included Amoxillin, Ampicillin, Cephalexin, Chloroquine, Ciprofloxacin, Dactinomycin, Levofloxacin, and Rifampicin; Salicylates included Aspirin; and other NSAIDS(excluded Aspirin) included Diclofenac, Ibuprofen, and Mefenamic acid. We identified these medications from the following NHI databases: Details of inpatient orders (DO), Details of ambulatory care orders (OO), Details of prescriptions dispensed at contracted pharmacies (GO); and coded following the medication code book in NHI website (http://www.nhi.gov.tw/Query/query1.aspx?menu=18&menu_id=703). The above medications prescribed before the BP onset were evaluated. Taking the time lag of BP onset and date of diagnosis into account, the use of each type of medication 2-12 months before onset was

Table 1-1. ***BP Incidence in Taiwan, 1998-2011***

Year	Male				Female				Total				RR
	BP(n)	Pop.(N)	C. Inc.	S. Inc.	BP(n)	Pop.(N)	C. Inc.	S. Inc.	BP(n)	Pop.(N)	C. Inc.	S. Inc.	M vs. F
1998	6	504110	1.19	1.28	6	477143	1.26	1.46	12	981253	1.22	1.34	0.88
1999	10	510447	1.96	1.99	12	482908	2.48	2.36	22	993355	2.21	2.15	0.84
2000	16	513836	3.11	2.80	17	486094	3.50	3.18	33	999930	3.30	3.04	0.88
2001	16	513836	3.11	2.71	17	486094	3.50	3.15	33	999930	3.30	2.89	0.86
2002	14	511285	2.74	2.09	15	483493	3.10	2.44	29	994778	2.92	2.23	0.86
2003	25	493197	5.07	3.48	13	476009	2.73	1.96	38	969206	3.92	2.75	1.77
2004	14	483923	2.89	1.83	4	466827	0.86	0.68	18	950750	1.89	1.28	2.70
2005	17	494871	3.44	1.99	14	475714	2.94	1.66	31	970585	3.19	1.83	1.20
2006	30	495784	6.05	3.73	16	475944	3.36	2.09	46	971728	4.73	2.90	1.78
2007	32	495673	6.46	4.01	18	475777	3.78	2.03	50	971450	5.15	3.03	1.98
2008	28	496021	5.64	3.49	22	475626	4.63	2.10	50	971647	5.15	2.80	1.67
2009	28	495297	5.65	2.92	26	475469	5.47	2.76	54	970766	5.56	2.84	1.06
2010	30	494860	6.06	2.79	25	475409	5.26	2.33	55	970269	5.67	2.57	1.19
2011	31	495040	6.26	2.70	26	475450	5.47	2.35	57	970490	5.87	2.50	1.15

BP(n): numbers of incident BP cases; Pop(N): Total population numbers; C. Inc.: Crude Incidence; S. Inc.: Standardized Incidence; RR: Incidence Rate Ratio; M vs. F: Male` vs. Female

Table 1-2. ***BP Incidence by age in Taiwan***

Age	≦50				50-59				60-69				70+			
Year	BP (n)	Pop. (N)	Inc.	RR	BP (n)	Pop. (N)	Inc.	RR	BP (n)	Pop. (N)	Inc.	RR	BP (n)	Pop. (N)	Inc.	RR
Male	35	5035420	0.70	0.021	43	1040081	4.13	0.127	66	452691	14.58	0.448	153	469988	32.55	Ref
Female	29	4844845	0.60	0.017	31	1019446	3.04	0.088	31	420801	7.37	0.212	140	402865	34.75	Ref
Total	64	9880265	0.65	0.019	74	2059527	3.59	0.107	97	873492	11.10	0.331	293	872853	33.57	Ref

BP(n): numbers of incident BP cases; Pop(N): Total population numbers; Inc.: Crude Incidence; RR: Incidence Rate Ratio

Table 2-1. ***Associations of pre-medication in 2-12 months and incident post-BPs in male and female***

Drug use	Gender	CS	Pre-medication 2-12months CN	OR(95% CI)	P
Antihypertensive (Yes/No)	Female	81/231	264/924	1.39(1.01-1.92)	0.044
	Male	100/297	295/1188	1.57(1.18-2.08)	0.0018
	Total	181/528	559/2112	1.49(1.20-1.84)	0.0002
Antibiotic (Yes/No)	Female	139/231	352/924	2.40(1.79-3.22)	<0.0001
	Male	180/297	475/1188	2.31(1.78-3.01)	<0.0001
	Total	319/528	827/2112	2.35(1.93-2.86)	<0.0001
Diuretic (Yes/No)	Female	59/231	121/924	2.40(1.66-3.46)	<0.0001
	Male	71/297	148/1188	2.31(1.66-3.21)	<0.0001
	Total	130/528	269/2112	2.35(1.84-3.00)	<0.0001
Other NSAID (Yes/No)	Female	99/231	445/924	0.81(0.60-1.08)	0.1483
	Male	134/297	534/1188	1.01(0.78-1.30)	0.9581
	Total	233/528	979/2112	0.91(0.75-1.11)	0.3566
Salicylate (Yes/No)	Female	58/231	143/924	1.93(1.34-2.77)	0.0004
	Male	97/297	246/1188	1.93(1.44-2.58)	<0.0001
	Total	155/528	389/2112	1.93(1.53-2.42)	<0.0001

coded yes or no.

Statistical Analysis

We used SAS Version 9.4 for Windows (SAS Institute, Inc., Cary, NC) for all analyses. The first diagnostic date of BP was used to calculate and determine the age of onset. To show the characteristics of BP and non-BP groups, student's t test and standard method for analyzing contingency r x c tables were used, and p values of t test and chi-square test were provided. $P<0.05$ indicated statistical significance.

Conditional logistic regressions for a nested case–control study were performed to calculate the Odds Ratio (OR) and 95% Confidence Interval (CI), to estimate the magnitude of the associations between correlated factors and BP.

Results

BP Incidence in Taiwan

Table 1-1 shows the BP incidence in male and female from year 1998 to year 2011. Incidences were standardized to world standardized population. The crude incidences are fluctuated from year 1998 to 2011, the standardized incidences range 1.28-4.01 per 100,000 in male, range 0.68-3.18 per 100,000, and range 1.28-3.04 in total population. The gender differences in standardized incidences are not consistent across these 14 years, year 1998-2011.

Table 1-2 shows the BP incidence in 4age groups, <=50, 50.1-59, 60-69, and>=70. BP incidences increase sharply as aging in both males and females, from 0.7 per 100,000 (age<=50) to 32.55 per 100000 (age>=70) in male (Rate Ratio=0.021, age>=70 as reference group) and from 0.6 per 100,000 (age<=50) to 34.75 per 100000 (age>=70) in female (Rate Ratio=0.017, age>=70 as reference group). Compared to age<=50 group,

Table 2-2. ***Associations of pre-medication in 2-12 months and incident post-BPs in male and female***

Drug use	Age group	CS	Pre-medication 2-12months		
			CN	OR(95% CI)	P
Antihypertensive (Yes/No)	<65	34/138	55/552	3.47(2.03-5.93)	<0.0001
	65-74	40/97	108/388	1.81(1.14-2.87)	0.0118
	>=75	107/293	396/1172	1.13(0.86-1.48)	0.3743
Antibiotic (Yes/No)	<65	76/138	216/552	1.96(1.33-2.88)	0.0006
	65-74	58/97	144/388	2.40(1.54-3.76)	0.0001
	>=75	185/293	467/1172	2.54(1.95-3.30)	<0.0001
Diuretic (Yes/No)	<65	15/138	16/552	4.19(1.98-8.87)	0.0002
	65-74	20/97	50/388	1.75(0.98-3.10)	0.0564
	>=75	95/293	203/1172	2.33(1.74-3.12)	<0.0001
Other NSAID (Yes/No)	<65	85/138	257/552	1.85(1.26-2.72)	0.0018
	65-74	47/97	183/388	1.05(0.67-1.65)	0.8184
	>=75	101/293	539/1172	0.62(0.47-0.81)	0.0004
Salicylate (Yes/No)	<65	18/138	32/552	2.68(1.40-5.14)	0.0030
	65-74	33/97	84/388	1.89(1.16-3.09)	0.0110
	>=75	104/293	273/1172	1.83(1.38-2.41)	<0.0001

BP incidences in age>=70 group are 50-60 folds higher.

Associations of medications and BP incidences

Table 2-1 shows the association of medications and BP incidences, stratified by gender. Associations of medications and BP incidences are not significantly different between men and women. Odds Ratios (OR) of antibiotics, diuretic, salicylate, and anti-hypertensive to BP incidence are 2.35, 2.35, 1.93, and 1.49, respectively. Other NSAID is not associated with incident BP.

Table 2-2 shows the association of medications and BP incidences, stratified by age groups. Considering sample sizes in each age groups, three age groups, age<65, age 65-74, and age>=75 are classified. Antibiotics are strongly associated with BP incidents in all age groups, ORs range from 1.96 to 3.03. Salicylates are also significantly associated with BP incidents in all age groups, ORs range 1.54-3.45. Associations of diuretics and BP incidents are different in three age groups, diuretics are not associated with BP incidents in age 65-74; the most significant association is in age<65 group, ORs is 4.19, corresponding to pre-medication 2-12 months. Anti-hypertensive show the strongest association with BP incidents only in age<65 group and decreased OR trends in 65-74 and age>=75 group, the ORs are 3.47, 1.81, 1.13. NSAIDs show the protected effect with BPs, OR=0.62, in age>=75.

Associations of neurological comorbidities and BP incidences

Tables 3-1 and 3-2 show the associations of neurological comorbidities and BP incidents stratified by age and gender. All four neurological disorders, stroke, dementia, Parkinson, epilepsy, are associated with BPs, and ORs are 5.65, 6.76, 3.75, and 5.00, respectively.

Table 3-1. ***Associations of neurological comorbidities and BP incidents by gender***

Neurological disorder	Gender	CS	CN	OR(95% CI)	P
Stroke (Yes/No)	Female	38/231	21/924	7.78(4.48-13.51)	<0.0001
	Male	47/297	48/1188	4.57(2.95-7.07)	<0.0001
	Total	85/528	69/2112	5.65(4.02-7.93)	<0.0001
Dementia (Yes/No)	Female	50/231	44/924	6.21(3.86-10.00)	<0.0001
	Male	57/297	48/1188	7.34(4.55-11.85)	<0.0001
	Total	107/528	92/2112	6.76(4.83-9.47)	<0.0001
Parkinson (Yes/No)	Female	18/231	2/924	3.71(1.92-7.16)	<0.0001
	Male	25/297	28/1188	3.79(2.17-6.61)	<0.0001
	Total	43/528	49/2112	3.75(2.45-5.74)	<0.0001
Epilepsy (Yes/No)	Female	10/231	6/924	6.67(2.42-18.34)	0.0002
	Male	13/297	13/1188	4.18(1.90-9.19)	0.0004
	Total	23/528	19/2112	5.00(2.70-9.29)	<0.0001

In table 3-1, ORs of stroke and epilepsy with BPs are 7.78 and 6.67 in female, higher than in male whose ORs are 4.57 and 4.18. By contrast, association of dementia and BPs is stronger in male, OR=7.34, than 6.21 in female. Associations of Parkinson and BPs are homogeneously, ORs=3.79 and 3.71 in male and in female, respectively. In table 3-2, associations of stroke and epilepsy with BPs are stronger in age group under 65 years old than in other age groups, ORs=32.00 and 12.00, respectively. Associations of dementia and Parkinson with BPs are the most significant in 65-74 age group, ORs=21.11 and 8.47, respectively.

Discussion

The BP incidences in this study is comparable to that in Chen et al., who reported an annual prevalence of 2.7 per 100,000[27]in Taiwan. Compare to the developed European countries, incidences of the same age group were higher in Taiwan than in German, Scotland, and UK. In Taiwan, incidence is 3.59 per 100,000 in the age group 50-59,around 20-25 folds higher than incidence 1-2/million in age group under 60 years old in Scotland[7]. Similarly, in age group 60-69, incidence is 11.10 per 100,000 in Taiwan, comparing to 0.7 per 100,000 in UK[1] 9.1/million in Germany[8], and 7-22/million in Scotland[7].Incidence of BP aged 60-69 are 5-15 folds high in Taiwan. Among the older people, incidence is 33.57 per 100,000 in age over 70 years old in Taiwan, comparing to 1.1-1.8 per 100,000 in age group 70-79 in UK[1], 24/million in age group 71-80 in Germany[8], and 31-51/million in age group 70-79 in Scotland. Taiwan's incidence are around 7-30 folds higher. Overall, Taiwan's BP incidences are 5-30 folds to developed European countries. The standardized incidence rates are not available for international comparison in the literatures. All these developed European countries have larger aging population than Taiwan does, the relative incidence rates for cross-country comparison might be even higher after standardization.

The associations between BP incidence and the medication used 2-12 months before BP onset are homogeneous between males and females, but heterogeneous in different age groups. Drug-induced bullous pemphigoid is characterized by a younger age of onset than that of the spontaneous occurred bullous pemphigoid[28]. Antihypertensive, diuretic, salicylate, and other NSAID, but not antibiotics, have larger Ors of BP

Table 3-2. ***Associations of neurological comorbidities and BP incidents by age***

Neurological disorder	Age	CS	CN	OR	P
Stroke (Yes/No)	<65	8/138	1/552	32.00(4.00-255.86)	0.0011
	65-74	13/97	11/388	5.01(2.19-11.46)	0.0001
	>=75	64/293	57/1172	5.21(3.55-7.66)	<0.0001
	Total	85/528	69/2112	5.65(4.02-7.93)	<0.0001
Dementia (Yes/No)	<65	1/138	1/552	4.00(0.25-63.95)	0.327
	65-74	17/97	5/388	21.11(6.16-72.31)	<0.0001
	>=75	89/293	86/1172	5.94(4.15-8.50)	<0.0001
	Total	107/528	92/2112	6.76(4.83-9.47)	<0.0001
Parkinson (Yes/No)	<65	4/138	4/552	4.70(1.03-21.39)	0.0452
	65-74	9/97	5/388	8.47(2.59-27.66)	0.0004
	>=75	30/293	40/1172	3.15(1.93-5.12)	<0.0001
	Total	43/528	49/2112	3.75(2.45-5.74)	<0.0001
Epilepsy (Yes/No)	<65	6/138	2/552	12.00(2.42-59.46)	0.0023
	65-74	1/97	5/388	0.80(0.09-6.85)	0.8386
	>=75	16/293	12/1172	5.64(2.61-12.18)	<0.0001
	Total	23/528	19/2112	5.00(2.70-9.29)	<0.0001

in people <65 than in older groups. It is possible that the Taiwanese have higher proportion of drug-induced BP, but we need more clinical details to differentiate and to estimate the attributable risk of drug-induced BPs[28].

Diuretics are associated with BP in this study, as reported by Lloyd-Lavery[14] et al. and Stavropoulos[28] et al. Among the diuretics, Loop diuretics, but not Thiazide and Spironolactone diuretics, are significantly associated with BP[14]. It was proposed that Theories have been proposed that the drug acting as an antigenic hapten or immune dysregulation might be related to the development of BP[29].

Antibiotics were more commonly prescribed to BP patients in this study might reflect that general clinicians treat symptoms before referring to a specialist for BP diagnosis[14]. Further analysis to study the duration of antibiotic use may elucidate this hypothesis.

Salicylates and antihypertensives were associated with BP, but few literatures mentioned their pathogenesis. In general, drug-induced BP might be related to anti-basement membrane antibody formation[30], accidental dysregulation or immune reorganization[31], molecular mimicry[32], and antigenic haptens[16]. In this study, we highlighted the association of common medications in the older population and BP incidence. Further pharmacological studies are needed to verify the mechanism and to develop the guidelines for the related drug prescriptions.

Incidence of BP is high among patients with neurological disorders. Patients with dementia, stroke, epilepsy, and Parkinson disease showed significant ORs for BP, ORs=6.76, 5.65, 5.00, 3.75, respectively. These findings might support the hypothesis that an autoimmune response to the neuronal isoform of BPAG1 and secondarily trigger an autoimmune response against the epithelial isoform of BPAG1[33-35]. Though our results are similar to the previous Taiwan study[27], the nested

case-control and age- sex- matching design further validate the association.

There are at least some limitations of this study. First, we did not investigate detailed medications of older people comprehensively. Second, a statistically acceptable sample size limited our stratification analysis of medications and neurological disorders. Third, we cannot confirm the causal relationships of BP and neurological disorders, and further studies are needed to elucidate the causal direction of BP and neurological disorders.

In conclusion, BP incidences in Taiwan are 5-30 folds higher than in the developed European countries. The drug uses, diuretic, salicylate, NSAID, and antihypertensive, are associated with incident BP; and neurological comorbidities are highly associated with BP. Further studies that adjust neurologic disorders co-morbidity and medications, especially to specific drug item, are needed to elucidate the causality of clinical factor to incident BPs.

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