The Association Between Bullous Pemphigoid and Neurological Disorders in A Selected Malaysian Population

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SUMMARY

Background: An association of bullous pemphigoid with neurological disorders has been reported. The objectives of this study were to review the clinical characteristics of patients with bullous pemphigoid and compare the association between bullous pemphigoid and various neurological disorders and comorbidities.

Methods: This was a retrospective case-control study involving 43 patients with bullous pemphigoid and 43 age-, sex- and ethnicity-matched controls.

Results: There was a statistically significant association between bullous pemphigoid and neurological disorders [Odds Ratio (OR) = 3.5, 95% Confidence Interval (CI) 1.3 to 9.2, p=0.011 and adjusted OR=3.5, 95% CI 1.2-10.3, p=0.026], in particular for dementia (p=0.002). Although stroke was more common among patients with bullous pemphigoid, this association was not statistically significant with OR of 1.9 (95% CI 0.7 to 5.2) and adjusted OR of 2.1 (95% CI 0.6 to 7.2). Similarly both ischaemic stroke (OR 1.5, 95% CI 0.5 to 4.2) and haemorrhagic stroke (OR 1.5, 95% CI 0.2 to 9.7) were more common. Other neurological disorders more common among patients with bullous pemphigoid were Parkinson's disease and epilepsy. Dyslipidaemia was significantly less common among patients with bullous pemphigoid (OR 0.4, 95% CI 0.1 to 0.9, p=0.033).

Conclusion: A combination of an inflammatory process, prothrombotic state and endothelial activation leads to an increased frequency of neurological disorders among patients with bullous pemphigoid. Thus, a holistic approach to patient care, including screening for dementia and control of comorbidities, should be practised as bullous pemphigoid affects more than just the skin.

KEY WORDS:
Immunobullous disease, internal disease associated with dermatology, epidemiology

INTRODUCTION

Bullous pemphigoid is an immunobullous disease which affects the elderly.[1] Clinical manifestations include pruritus and urticated, erythematous lesions which later develop into large, tense subepidermal blisters and mucosal involvement. An association of bullous pemphigoid with neurological diseases such as stroke, dementia, Parkinson's disease, epilepsy, amyotrophic lateral sclerosis, syringomyelia and multiple sclerosis has been reported.[1-7]

Several mechanisms have been postulated to explain the association between bullous pemphigoid and neurological disorders. Firstly, in terms of immunology and inflammation, neuronal isoforms of BP180 and 230 antigens lead to cross-reactivity between the skin and the brain.[1,2] This process is further facilitated by damage to the blood-brain barrier due to the neurological disorder.[1] Systemic inflammation involving the T helper 1 and T helper 2 immune responses has also been found in bullous pemphigoid as evidenced by elevated serum levels of cytokines.[3, 8-11]

Secondly, there is a prothrombotic state due to antiphospholipid antibodies and an increase in plasminogen activator inhibitor type 1 (PAI-1) activity and antigen.[3, 12, 13] Thirdly, increased serum levels of soluble E-selectin (induced by tumour necrosis factor-α and IL-10)[9] and vascular endothelial growth factor play a role in endothelial activation and immune reactions.[14, 15] These processes ultimately cause atherosclerosis, plaque rupture, thrombosis and stroke.[3, 13, 16-18]

This study aimed to review the clinical characteristics of patients with bullous pemphigoid and compare the association between bullous pemphigoid and various neurological disorders and comorbidities.

MATERIALS AND METHODS

This was a retrospective case-control study involving 43 patients diagnosed with bullous pemphigoid based on the International Coding of Diseases (ICD) 694.5 seen in the Dermatology Unit from 2004 to 2013. The case notes were reviewed and indicated whether the diagnosis of bullous pemphigoid was confirmed histopathologically and/or via direct immunofluorescence. Clinical characteristics, demographics and treatment of these patients were reviewed. Approval was obtained from the hospital's Medical Ethics Committee.

The presence of various comorbidities, particularly neurological disorders, were compared with 43 age-,

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Table I: Comparison of neurological disorders and comorbidities between cases of bullous pemphigoid and controls

Disease	Number of bullous pemphigoid cases (%)	Number of controls (%)	Odds ratio (OR)	95% confidence interval (CI)	p-value
Neurological disorders	19 (44.2%)	8 (18.6%)	Crude OR 3.5 Adjusted OR 3.5	1.3-9.2 1.2-10.3	0.011 0.026
Dementia	9 (20.9%)	0 (0.0%)	-	-	0.002
Stroke	13 (30.2%)	8 (18.6%)	Crude OR 1.9 Adjusted OR 2.1	0.7-5.2 0.6-7.2	0.209 0.237
Ischaemic stroke	11 (25.6%)	8 (18.6%)	Crude OR 1.5 Adjusted OR 1.7	0.5-4.2 0.5-5.8	0.436 0.423
Haemorrhagic stroke	3 (7.0%)	2 (4.7%)	Crude OR 1.5 Adjusted OR 1.2	0.2-9.7 0.1-10.2	1.000 0.872
Parkinson's disease	1 (2.3%)	0 (0.0%)	-	-	1.000
Epilepsy	2 (4.7%)	0 (0.0%)	-	-	0.494
Risk factors					
Diabetes mellitus	22 (51.2%)	17 (39.5%)	1.6	0.7-3.8	0.279
Arrhythmia	2 (4.7%)	1 (2.3%)	2.0	0.2-23.5	1.000
Hypertension	27 (62.8%)	28 (65.1%)	0.9	0.4-2.2	0.822
Coronary artery disease	9 (20.9%)	12 (27.9%)	0.7	0.3-1.8	0.451
Dyslipidaemia	8 (18.6%)	17 (39.5%)	0.4	0.1-0.9	0.033
Other conditions					
Chronic kidney disease	6 (14.0%)	3 (7.0%)	2.2	0.5-9.3	0.483
Malignancy	2 (4.7%)	3 (7.0%)	0.7	0.1-4.1	1.000
Chronic lung disease	5 (11.6%)	5 (11.6%)	1.0	0.3-3.7	1.000
Mood disorder	2 (4.7%)	2 (4.7%)	1.0	0.1-7.4	1.000
Other psychiatric disorders	2 (4.7%)	1 (2.3%)	2.0	0.2-23.5	1.000

* Obtained from Wald chi-squared test (binary logistic regression)

ethnicity- and sex-matched controls (who did not have bullous pemphigoid) obtained from the Dermatology Clinic database using random number tables. The medical records for both cases and controls were reviewed. Radiological findings for patients with cerebrovascular disease were also reviewed. Statistical analysis was carried out using SPSS version 21.0. Binary logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI) for various neurological disorders and comorbidities. Pearson chi-squared or Fisher's exact test were used to calculate p values with a statistical significant level of $p<0.05$. The adjusted odds ratio and the corresponding 95% confidence interval (95% CI) was also calculated for all neurological disorders, stroke, ischaemic stroke and haemorrhagic stroke with adjustment for sex, ethnicity, diabetes mellitus, hypertension, dyslipidaemia, arrhythmias and coronary artery disease. For the adjustments done, the Wald chi-squared test was used instead.

RESULTS

A total of 43 patients with bullous pemphigoid were compared with age-, ethnicity- and sex-matched controls (Table I). There were 24 males (55.8%) and 19 females (44.2%) in each arm (p=1.000). Bullous pemphigoid was found mainly among the older age group, with median age of 79.4 years. The median age of the control group was similar at 79.6 years. The ethnic composition in both arms were similar, with 13 Malay patients (30.2%), 16 Chinese patients (37.2%) and 14 Indian patients (32.6%) in each arm (p=1.000).

Majority of the patients (76.7%, n=33) were diagnosed based on histopathological and direct immunofluorescence findings while four patients (9.3%) were diagnosed based on histopathological findings alone and two patients (4.7%) were diagnosed based on direct immunofluorescence findings. In four cases (9.3%), the diagnosis of bullous pemphigoid had been made at another institution and detailed skin biopsy reports were not available.

In our study population, 86.0% (n=37) of lesions were found on the lower limbs followed by 81.4% (n=35) on upper limbs. 69.8% of patients (n=30) reported pruritus. Only 11.6% (n=5) had mucosal involvement. For atrophic scarring, alopecia and milia, only 2.3% (n=1) reported these findings. 97.7% (n=42) of patients were prescribed with oral prednisolone while 23.3% (n=10) of patients were prescribed a combination of oral prednisolone with oral azathioprine. One patient was lost to follow-up even prior to the commencement of treatment.

Table I shows the comparison of various neurological disorders and comorbidities between patients with bullous pemphigoid and controls. Neurological disorders in general were found to have a statistically significant association with bullous pemphigoid (Crude OR 3.5, 95% CI 1.3 to 9.2 and adjusted OR 3.5, 95% CI 1.2 to 10.3).

Table II: Association of bullous pemphigoid and various neurological disorders in previous studies

Study	All neurological disorders	Cerebrovascular disease	Stroke	Epilepsy (Seizures in Brick's study)	Dementia	Parkinson's disease
Our study	44.2% OR 3.5 (95% CI 1.3-9.2) p=0.011	N.A.	30.2% OR 1.9 (95% CI 0.7-5.2) p=0.209	4.7% - p=0.494	20.9% - p=0.002	2.3% - p=1.000
Brick *et al.* J Am Acad Dermatol[7] (previous diagnosis)	23% OR 6.85 (95% CI 3.00-15.64) p<0.001	6% OR 3.00 (95% CI 0.87-10.36) p=0.08	N.A.	3% OR 11.54 (95% CI 1.24-infinity) p=0.01	10% OR 6.75 (95% CI 2.08-21.92) p=0.002	3% OR 9.00 (95% CI 0.94-86.52) p=0.06
Cai *et al.* Brit J Dermatol 2014[23]	-	N.A.	40.4%	-	23.7%	10.3%
Teixeira, Cabral, Brites, Vieira, Figueiredo An Bras Dermatol 2014[5]	55.8% OR 5.36 (95% CI 2.97-9.66) p<0.001	N.A.	35.1% OR 8.10 (95% CI 3.80-17.25) p<0.001	-	37.7% OR 5.25 (95% CI 2.71-10.16) p<0.001	5.2% OR 4.91 (95% CI 0.88-27.44) p=0.046
Zhang *et al.* Eur J Dermatol 2013[21]	-	42.55%	-	-	-	-
Yang *et al.* Stroke 2011[3]	-	N.A.	22.8% HR 2.37 (95% CI 1.78-3.15)	-	-	-
Chen *et al.* Brit J Dermatol 2011[2]	-	N.A.	36.8% OR 3.30 (95% CI 3.03-3.60)	5.8% OR 3.97 (95% CI 3.28-4.81)	17.7% OR 4.81 (95% CI 4.26-5.42)	11.9% OR 3.49 (95% CI 3.05-3.98)
Langan, Groves and West J Invest Dermatol 2011[4]	-	N.A.	8% OR 1.8 (95% CI 1.3-2.5) p<0.001	2% OR 1.7 (95% CI 1.0-3.0) p=0.05	7% OR 3.4 (95% CI 2.4-4.8) p<0.001	3% OR 3.0 (95% CI 1.8-5.0) p<0.001
Taghipour *et al.* Arch Dermatol 2010*[1]	46% OR 6.8 (95% CI 3.5-13.3) Adjusted OR 6.2 (95% CI 3.1-12.4)	30% OR 6.3 (95% CI 2.8-14.2) Adjusted OR 6.0 (95% CI 2.6-13.6)	N.A.	4% OR 6.5 (95% CI 0.7-59.2) Adjusted OR 7.8 (95% CI 0.8-72.4)	13% OR 10.7 (95% CI 2.3-49.0) Adjusted OR 7.9 (95% CI 1.7-37.3)	4% OR 2.7 (95% CI 0.6-11.6) Adjusted OR 2.6 (95% CI 0.6-11.4)
Cordel et al. Dermatology 2007[6]	36%	N.A.	15% (95% CI 11-19%)	-	20% (95% CI 16-25%)	9% (95% CI 7-13%)

*Adjusted for age and sex
HR = hazard ratio, OR = odds ratio, CI = confidence interval, N.A. = not applicable

There was a statistically significant association between bullous pemphigoid and dementia (p=0.002). Ischaemic and haemorrhagic stroke, Parkinson's disease and epilepsy were more likely to occur among patients with bullous pemphigoid as compared to controls (Table I).

With regards to factors contributing towards the risk of stroke, only diabetes mellitus and arrhythmias were more common among bullous pemphigoid patients. Hypertension, dyslipidaemia and coronary artery disease were less common, with only the negative association with dyslipidaemia being statistically significant (p=0.033).

In our study population, chronic kidney disease was more common among patients with bullous pemphigoid while malignancy was less common compared to controls. However, none of these results were statistically significant.

Table III: Cardiovascular risk factors among patients with bullous pemphigoid

Study	Diabetes mellitus	Hypertension	Dyslipidaemia	Coronary artery disease
Our study	51.2%	62.8%	18.6%	20.9%
Cai *et al.* Brit J Dermatol 2014[23]	32.6%	59.3%	-	22.0%
Zhang *et al*. Eur J Dermatol 2013[21]	22.34%	39.36%	6.9%	-
Kulthanan *et al.* Asian Pac J Allergy Immunol 2011[22]	19%	41.4%	-	-
Yang, Chen, Xirasagar, Lin Stroke 2011[3]	17.2% (p=0.013)	30.5% (p=0.132)	5.1% (p=0.120)	9.5% (p=0.674)

CI = confidence interval

There were no patients with chronic liver disease, hereditary peripheral neuropathies, Shy-Drager syndrome, multiple sclerosis and inflammatory or toxic neuropathies among either the cases or the controls.

DISCUSSION

In this study, neurological disorders were more frequent among patients with bullous pemphigoid (n=19, 44.2%) with stroke (30.2%) and dementia (20.9%) being the two most common. However, only the associations with all neurological disorders (p=0.011) and dementia (p=0.002) achieved statistical significance. These findings were consistent with other studies, as shown in Table II.[1-2, 4-5]

Although the number of bullous pemphigoid patients with stroke was higher than those with dementia, only the association with dementia was significant. Stroke is a common disease among the older age group and these patients tend to present acutely to healthcare institutions while dementia tends to be a culturally acceptable part of ageing in the local context and is a more insidious process.

Common risk factors which link Alzheimer's disease (which is a common cause of dementia) and intracranial atherosclerosis include apoEe4 polymorphism, hypercholesterolaemia, hypertension, hyperhomocysteinaemia, diabetes mellitus, metabolic syndrome, smoking, systemic inflammation, increased fat intake and obesity.[19] Infection and inflammation may induce the expression of cholesterol 25-hydroxylase (CH25H). Chronically, the macrophage enzymatic product (25OHC) activates acyl-CoA cholesterol acyltransferase (ACAT) causing cholesterol esterification, lipid droplet formation and ultimately leading to vascular occlusion.[20] Atherosclerosis and vascular occlusion can also lead to vascular or 'multi-infarct' dementia, caused by a series of small strokes and which may overlap with Alzheimer's disease.

Table II shows previous studies in which the authors found a significant association between bullous pemphigoid and stroke or cerebrovascular disease.[1-5] The studies by Chen, Yang and Langan were population-based.[2-4] Previous studies also found a significant association between bullous pemphigoid and epilepsy, dementia and Parkinson's disease as shown in Table II. Cordel *et al.* also noted a significant association with multiple sclerosis, amyotrophic lateral sclerosis and syringomyelia at 5% (3-9%)[6] while Langan, Groves and West also noted a significant association with multiple sclerosis with 8% of patients, OR 10.7 (95% CI 2.8-40.2, p<0.001).[4] Brick et al. noted a statistically significant risk of developing neurological disorders following a diagnosis of bullous pemphigoid with a hazard ratio (HR) of 2.02 (95% CI 1.17-3.49, p=0.01), notably Parkinson disease with a hazard ratio of 8.56 (95% CI 1.55-47.25, p=0.01).[7]

Table III shows the rates of diabetes mellitus, hypertension and dyslipidaemia in previous studies by Zhang *et al.*,[21] Kulthanan *et al.*[22] and Yang, Chen, Xirasagar and Lin.[3] The profile of comorbidities in our study was fairly similar to a study done by Cai *et al.* in our neighbouring country Singapore.[23] The association between bullous pemphigoid and primary diabetes mellitus was shown in a study by Chuang *et al.* in which the occurrence rate was 20% among the bullous pemphigoid patients (prior to treatment with systemic corticosteroids) and 2.5% among the controls (p=0.004).[24] Although the bullous pemphigoid patients in our study had higher rates of cardiovascular risk factors, the rates of stroke and dementia reported in our cohort were fairly similar, if not even lower than some of the previously reported studies. This may imply that the underlying mechanism may not be so much related to the conventional atherosclerosis process alone and immune-mediated processes may play a large part as well.

The rates of concurrent malignancies were 4% in the study by Langan, Groves and West, 8.6% in the study by Kulthanan et al. and 13.4% in the study by Cai *et al.*[4, 22, 23] The proportion of bullous pemphigoid patients who had kidney disease in previous studies by Cai *et al*. was 11.4% and by Langan, Groves and West was 19%.[4, 23]

The limitations of our study include a retrospective design. The sampling was also hospital-based, from a single centre. It would be ideal to study these associations using a population-based database. The severity of the cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidaemia and the presence of other risk factors which may play a role in the pathogenesis of stroke such as obesity, alcohol consumption, smoking and dietary habits were not assessed. The role of corticosteroid therapy for bullous pemphigoid as a possible confounding factor leading

to increased risk of neurological disorders was unable to be defined. The types of dementia were also not defined in our records. For patients diagnosed at other institutions, the detailed histopathology and immunofluorescence reports were not available due to the retrospective nature of the study.

CONCLUSION

The association between bullous pemphigoid and neurological disorders can be explained by a combination of an inflammatory process, prothrombotic state and endothelial activation. It is imperative to adopt a holistic approach to patient care in view of the increased rates of neurological disorders among bullous pemphigoid patients. Dementia screening can be done with the aid of questionnaires in the clinical setting, such as the Mini Mental State Examination (MMSE). Referrals to relevant specialties such as Neurology or Geriatrics may be necessary. Control of lifestyle factors and comorbidities should be emphasised in the treatment of bullous pemphigoid patients as a preventive measure against neurological disorders such as stroke and dementia.

REFERENCES

1. Taghipour K, Chi CC, Vincent A, *et al.* The Association of Bullous Pemphigoid with Cerebrovascular Disease and Dementia. Arch Dermatol 2010; 146(11): 1251-4.
2. Chen YJ, Wu CY, Lin MW, *et al.* Comorbidity profiles among patients with bullous pemphigoid: a nationwide population-based study. Brit J Dermatol 2011; 165(3): 593-9.
3. Yang YW, Chen YH, Xirasagar, S *et al.* Increased Risk of Stroke in Patients with Bullous Pemphigoid: A Population-Based Follow-Up Study. Stroke 2011; 42(2): 319-23.
4. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: A population-based case-control study. J Invest Dermatol 2011; 131(3): 631-6.
5. Texeira VB, Cabral R, Brites MM, *et al.* Bullous pemphigoid and comorbidities: a case-control study in Portuguese patients. An Bras Dermatol 2014; 89(2): 274-8.
6. Cordel N, Chosidow O, Hellot MF, *et al.* Neurological disorders in patients with bullous pemphigoid. Dermatology 2007; 215(3): 187-91.
7. Brick KE, Weaver CH, Savica R et al. A population-based study of the association between bullous pemphigoid and neurological disorders. J Am Acad Dermatol 2014; 71(6): 1191-7.
8. Nakashima H, Fujimoto M, Asashima N, *et al.* Serum chemokine profile in patients with bullous pemphigoid. Brit J Dermatol 2007; 156(3): 454–9.
9. Echigo T, Hasegawa M, Shimada Y, *et al.* Both Th1 and Th2 chemokines are elevated in sera of patients with autoimmune blistering diseases. Arch Dermatol Res 2006; 298(1): 38-45.
10. Inaoki M, Takehara K. Increased serum levels of interleukin (IL)-5, IL-6 and IL-8 in bullous pemphigoid. J Dermatol Sci 1998; 16(2): 152–7.
11. D'Auria L, Pietravalle M, Mastroianni A, *et al.* IL-5 levels in the serum and blister fluid of patients with bullous pemphigoid: correlations with eosinophil cationic protein, RANTES, IgE and disease severity. Arch Dermatol Res 1998; 290(1-2): 25–7.
12. Riboldi P, Gerosa M, Raschi E, *et al.* Endothelium as a target for antiphospholipid antibodies. Immunobiology 2003; 207(1): 29 –36.
13. Marzano AV, Tedeschi A, Polloni I, *et al.* Prothrombotic state and impaired fibrinolysis in bullous pemphigoid, the most frequent autoimmune blistering disease. Clin Exp Immunol 2013; 171(1): 76-81.
14. Ameglio F, D'Auria L, Cordiali-Fei P, *et al.* Bullous pemphigoid and pemphigus vulgaris: correlated behaviour of serum VEGF, sE-selectin and TNF-alpha levels. J Biol Regul Homeost Agents 1997; 11(4): 148-53.
15. D'Auria L, Cordiali Fei P, Pietravalle M, *et al.* The serum levels of sE-selectin are increased in patients with bullous pemphigoid or pemphigus vulgaris. Correlation with the number of skin lesions and recovery after corsticosteroid therapy. Brit J Dermatol 1997; 137(1): 59-64.
16. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999; 340(2): 115–26.
17. Takeda H, Spatz M, Ruetzler C, *et al.* Induction of mucosal tolerance to E-selectin prevents ischemic and hemorrhagic stroke in spontaneously hypertensive genetically stroke-prone rats. Stroke 2002; 33(9): 2156–63.
18. Elkind MS. Inflammatory markers and stroke. Curr Cardiol Rep 2009; 11(1): 12–20.
19. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004; 363(9415): 1139-46.
20. Lathe R, Sapronova A, Kotelevtsev Y. Atherosclerosis and Alzheimer – diseases with a common cause? Inflammation, oxysterols, vasculature. BMC Geriatrics 2014; 14: 36.
21. Zhang LM, Wu J, Xiao T, *et al.* Treatment and mortality rate of bullous pemphigoid in China: a hospital-based study. Eur J Dermatol 2013; 23(1): 94-8.
22. Kulthanan K, Chularojanamontri L, Tuchinda P, *et al.* Prevalence and clinical features of Thai patients with bullous pemphigoid. Asian Pac J Allergy Immunol 2011; 29(1): 66-72.
23. Cai SCS, Allen JC, Lim YL, *et al.* Mortality of bullous pemphigoid in Singapore: risk factors and causes of death in 359 patients seen at the National Skin Centre. Brit J Dermatol 2014; 170(6): 1319-26.
24. Chuang TY, Korkij W, Soltani K, *et al.* Increased frequency of diabetes mellitus in patients with bullous pemphigoid: a case-control study. J Am Acad Dermatol 1984; 11(6): 1099-102.