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Original Article

Dermatology Section

Proportion of Co-morbidities in Patients with and without Bullous Pemphigoid: A Cross-sectional Study

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ABSTRACT

Introduction: Bullous Pemphigoid (BP) is the most common subepidermal immunobullous disorder. It has been found to be associated with various co-morbidities. Only a few studies have been done previously, to find out the association between BP and these co-morbidities. A better understanding of the various co-morbidities in BP patients, enables to implement better treatment strategies, which will be more efficacious and less toxic.

Aim: To compare the proportion of co-morbidities in patients with and without BP and to study the triggering factors associated with BP.

Materials and Methods: This was a hospital based cross-sectional study conducted in the Department of Dermatology and Venereology at Government Medical College and Hospital, Trivandrum, Kerala, India. The duration of the study was one year and six months, from January 2020 to June 2021. A total of 80 patients were included in the present study, out of which 40 patients with BP were included in case group and 40 patients without BP in control group. Clinical data such as age, gender, habits, co-morbidities and factors triggering BP were recorded. Categorical and quantitative variables were expressed as frequency (percentage) and mean±SD respectively. Chi-square test and Fisher's-exact test were used to find association between categorical variables and (p-value <0.05) was considered as statistically significant.

Results: The mean age of the study participants was 60.8±10.5 years. A total of 23 (57.5%) patients and 20 (50%) normal subjects had a history of co-morbid illness. Diabetes, hypertension, neurological disorders, Coronary Artery Disease (CAD) and Chronic Kidney Disease (CKD) were the co-morbidities reported by the patients. Diabetes was the most commonly observed co-morbidity among the patients. A statistically significant difference was noted between the case and control group in terms of diabetes (p-value=0.039) and neurological disorders (p-value=0.011). A total of 34 (85%) patients had atleast one factor which triggered the onset of the disease, and the most common triggering factor was drug intake in 22 (55%) patients.

Conclusion: The most commonly observed co-morbidity among patients with BP in the present study was diabetes. A prompt surveillance and adequate control of glycaemic status is needed in these patients in order to avoid further worsening of diabetes with corticosteroid therapy. Avoidance of various exogenous triggers such as disease worsening drugs, stress, excessive sun exposure etc., will help in achieving better control of the disease.

Keywords: Diabetes, Hypertension, Neurological, Triggering factor

INTRODUCTION

The BP is the most common subepidermal immunobullous disorder and represents the most frequent autoimmune blistering disease [1]. It mainly affects elderly people, although, younger patients may also be affected, and often starts with pruritus along with urticated and erythematous lesions. Later, tense blisters develop both, on erythematous and normal skin [2] along with mucosal involvement may be seen. The notable prevalence of BP in elderly patients with multiple co-morbidities has been stimulating research into their association with other diseases. The detection of co-morbidities in patients with Acute Behavioural Disturbances (ABDs) is therefore, important, both to favour optimal therapeutic management and to improve the patient's final prognosis. The co-morbidities commonly associated with BP are neuropsychiatric diseases, diabetes, hypertension, ischaemic heart disease, autoimmune diseases and the less common ones include thyroid disease, malignancies, Chronic Obstructive Pulmonary Disease (COPD), infections etc., [3]. BP patients are more prone to develop any neurological disorder, mainly multiple sclerosis, dementia, Parkinson's disease, epilepsy and stroke [4]. Hypertension and neurological diseases are also, the most common co-morbidities noted in BP patients [5,6].

Several trigger factors, such as drugs, thermal or electrical burns, surgical procedures, trauma, ultraviolet irradiation, radiotherapy, chemical preparations, transplants and infections may induce or exacerbate BP disease [7]. The putative drugs are antibiotics, beta-blockers, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), diuretics and, more recently, anti-Tumor Necrosis Factor alpha (TNF-α), Dipeptidyl Peptidase 4 inhibitors (DPP-4i). The pathogenesis of Drug Induced BP (DIBP) is controversial and often difficult to understand and to demonstrate. As, BP mostly affects elderly people, usually assuming several drugs, it is arduous to establish the triggering role of a specific medication. Systemic corticosteroids are effective in the treatment of BP. However, the use of systemic corticosteroids prolongs admission time for the patients and may worsen the pre-existing co-morbid illness. There is a paucity of studies, to find the association of BP with various co-morbidities and associated triggering factors. While, some studies are existing in the literature on the Indian population, to the best of the author's knowledge, no such study has been done from Kerala.

A better understanding of the various co-morbidities in BP patients will enable to implement better treatment strategies that will be more efficacious and less toxic. Hence, the present study was conducted to compare the proportion of co-morbidities in patients with BP, with those without BP and thereby, to determine the association between BP and these co-morbidities. The present study has also tried to find out the various triggering factors associated with BP.

MATERIALS AND METHODS

A hospital based cross-sectional study was done in the Department of Dermatology and Venereology at Government Medical College and Hospital, Trivandrum, Kerala, India, for a period of one year and six months, from January 2020 to June 2021. The study was conducted

after getting clearance from Institutional Ethics Committee (IEC No.12/05/2019/MCT.) The participants were given an information sheet explaining the details and purpose of the present study.

The study comprised 40 patients diagnosed with BP as the case group and 40 normal health subjects without BP, who accompanied the patients to Dermatology Department as the control group.

Inclusion criteria: All new cases of BP diagnosed clinically confirmed by skin biopsy and/or by a positive direct immunofluorescence test, and all consenting male and female patients without BP, belonging to the same age group, as cases and controls respectively, were included in the study.

Exclusion criteria: Patients not giving an informed consent and who were already on treatment were excluded from the study.

Sample size calculation: Sample size calculation was done by using a formula:

$$N=(Z1-\alpha/2+Z1-\beta)^2\ (P1Q1+P2Q2)/(P1-P2)^2,$$

where N is sample size, $(Z1-\alpha/2+Z1-\beta)^2$ value was 10.49, when α=5%, β=20%. P1=proportion of exposed among patients with BP, Q1=100-P1, P2=proportion of exposed among patients without BP, Q2=100-P2 [8], P1=(55.8%), P2=(20.5%) after applying in the formula, N=35. Therefore, 40 patients each, from both case and comparison groups were selected for the study.

Study Procedure

All the relevant clinical history including socio-demographic details, clinical symptoms, triggering factors such as, stress, food, physical trauma, chemical agents such as, pesticides and house cleaning products, sun exposure, radiotherapy, drugs, infections like, urinary tract infection, pulmonary infections etc., malignancies, vaccination, topical applications, habits such as, smoking and alcohol intake and relevant past history regarding the various self-reported co-morbidities and the medications used were recorded. A thorough cutaneous examination was carried out including nail, hair and mucosal surfaces and the relevant clinical signs of the disease such as Nikolsky's sign [9] and Asboe-Hansen sign [9] were elicited and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) [10] was calculated.

Severity of the disease was categorised, based on percentage of Body Surface Area (BSA) involvement as [11]: Mild=<10%, Moderate=10-30%, Severe=>30%. Systemic examination was done to rule out any associated disease. Complete blood count, Renal Function Test (RFT), Liver Function Test (LFT), Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), Fasting Lipid Panel (FLP), Chest X-ray, Ultrasonography (USG) abdomen, skin biopsy, direct immunofluorescent and other relevant investigations required to diagnose the disease was done. Also, the expert opinion from the concerned specialist was obtained when found necessary, for evaluation of these co-morbidities, and appropriate treatment for the same was started, as per the expert opinion. The same set of investigations were done in the comparison group also. Comparison of co-morbidities among patients with BP and the control group was done to find out the association of these co-morbidities with BP. Various triggering factors in BP patients were also assessed and their prevalence was studied, to find out the most common triggering factor.

STATISTICAL ANALYSIS

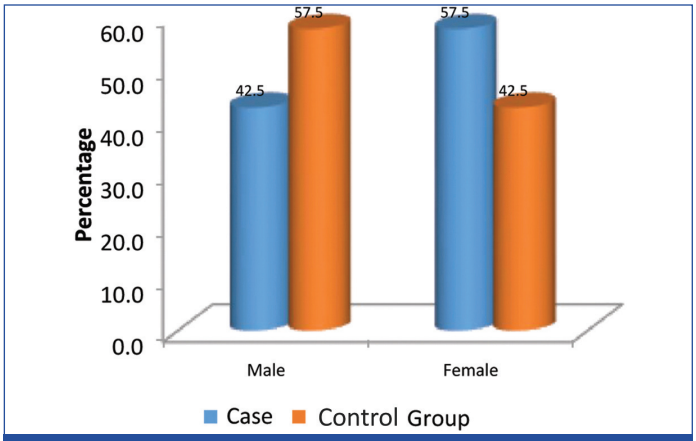
Statistical analyses was performed by using Statistical Package for Social Sciences (SPSS), version 20.0. Categorical and quantitative variables were expressed as frequency (percentage) and mean±SD, respectively. Chi-square test and Fisher's-exact test were used to find association between categorical variables. For all statistical interpretations (p-value <0.05) was considered the threshold for statistical significance.

RESULTS

A total of 40 patients with BP and 40 age group matched normal subjects were studied. Majority of the patients i.e., 8 (20%) patients belonged to the age group 56-60 years. Mean age of the study subjects was 60.8±10.5 years [Table/Fig-1]. A female preponderance was noted among the patients with BP in the present study, with M:F ratio of 1:1.35 [Table/Fig-2]. Majority of the cases and those among the comparison group were non smokers and non alcoholics. 4 (10%) cases were active smokers and 4 (10%) were chronic alcoholics, but there was no statistically significant difference in the occurrence of BP between the active smokers/chronic alcoholics and those without these habits. A total of 10 (25%) patients reported mucosal involvement. 25 (62.5%) patients had severe disease with more than 30% of BSA involvement. The mean ABSIS score was 51.72.

	Case group	Control group
Age (in years)	n (%)	n (%)
35-40	1 (2.5)	1 (2.5)
41-45	2 (5.0)	2 (5.0)
46-50	3 (7.5)	3 (7.5)
51-55	6 (15.0)	6 (15.0)
56-60	8 (20.0)	8 (20.0)
61-65	7 (17.5)	7 (17.5)
66-70	5 (12.5)	5 (12.5)
71-75	5 (12.5)	5 (12.5)
>75	3 (7.5)	3 (7.5)
Mean±SD	60.8±10.5	60.75 10.3

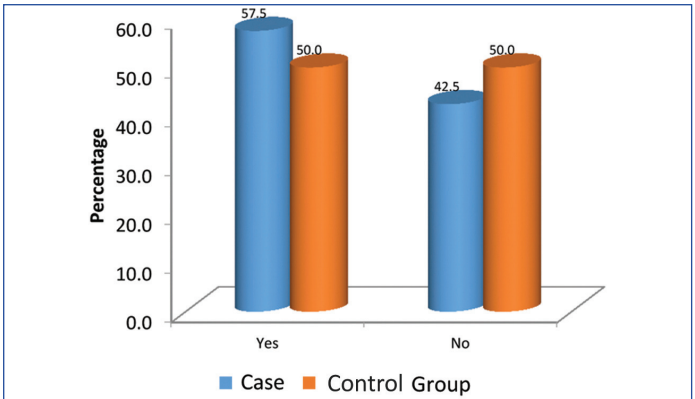
[Table/Fig-1]: Age distribution (N=80).
n= Number; %= Percentage



[Table/Fig-2]: Gender distribution.

A total of 23 (57.5%) cases and 20 (50%) normal subjects had a history of co-morbid illness that showed no statistical significance [Table/Fig-3]. Diabetes, hypertension, neurological disorders, CAD and CKD were the co-morbidities reported by the patients with BP [Table/Fig-4]. Diabetes was the most commonly observed co-morbidity, noted in 20 (50%) patients and a statistically significant difference was found between the cases and comparison group (p-value=0.039). Hypertension was the second most common co-morbidity seen in 16 (40%) cases control group with no statistically significant difference. The overall reported prevalence of neurological disorders among BP cases was 6 (15%) and a statistically significant difference was noted between the cases and comparison group (p-value=0.011). The neurological disorders reported were Cerebrovascular Accident (CVA), Parkinsonism and dementia.

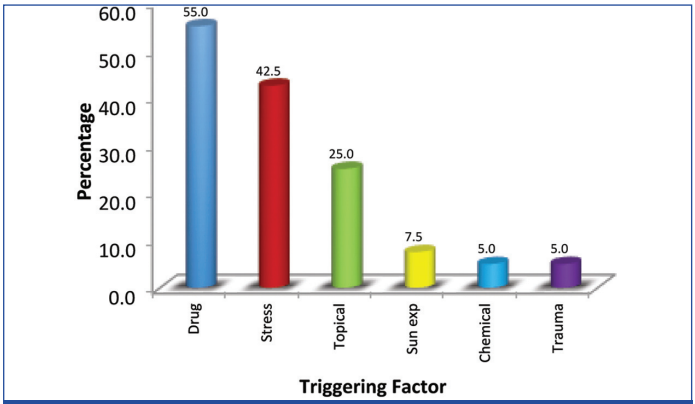
A total of 34 (85%) patients had atleast one factor which triggered the onset of the disease [Table/Fig-5]. The most common triggering factor was drug intake 22 (55%) patients [Table/Fig-6]. The most common group of drug used among cases was statins 15 (37.5%)



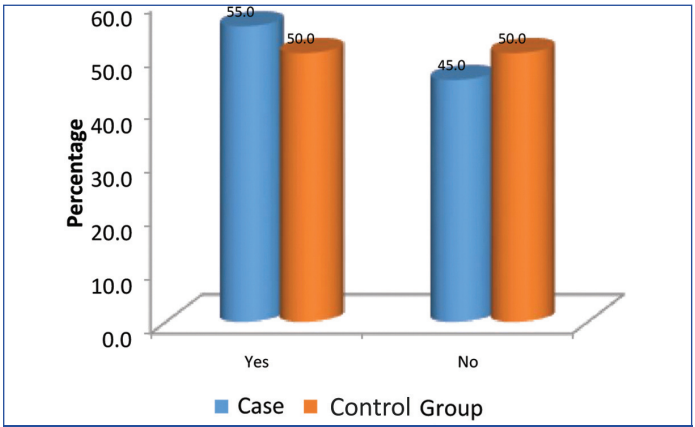
[Table/Fig-3]: Presence of co-morbidities among case and control group.

Co-morbid illness	Case group n (%)	Control group n (%)	Chi-square value	p-value
DM	20 (50)	11 (27.5)	4.27	*0.039
HTN	16 (40)	15 (37.5)	0.05	0.818
DM and HTN	10 (25)	6 (15)	1.25	0.264
CAD	2 (5)	2 (5)	0	1#
CKD	1 (2.5)	0	1.01	0.314#
CNS disease	6 (15)	0	6.49	*0.011

[Table/Fig-4]: Distribution of co-morbidities among case and control group.
DM: Diabetes mellitus; HTN: Hypertension; CAD: Coronary artery disease; CKD: Chronic kidney disease; CNS: Central nervous system
Test applied: Chi-square test and Fisher-exact test, *p-value <0.05
#Fischer-exact test *Chi-square test



[Table/Fig-5]: Factors triggering Bullous Pemphigoid (BP).



[Table/Fig-6]: History of drug intake among case and control group.

patients, followed by Angiotensin Converting Enzyme (ACE) inhibitors/Angiotensin Receptor Blockers (ARB) 14 (35%) patients and sulfonylureas 13 (32.5%) patients [Table/Fig-7]. Statistically significant difference was noted among cases and comparison group in usage of statins and ACE inhibitors/ARBs (p-value-=0.045) and (p-value=0.039), respectively. Only 1 (2.5%) patient gave history of usage of gliptins which was reportedly the most implicated drug for BP.

Drug	Case group n (%)	Control group n (%)	χ^2	p-value
Statin	15 (37.5)	7 (17.5)	4.01	*0.045
ACEi/ARB	14 (35)	6 (15)	4.27	*0.039
Beta-blocker	5 (12.5)	4 (10)	0.13	0.723
CCB	11 (27.5)	12 (30)	0.06	0.805
Sulfonylurea	13 (32.5)	9 (22.5)	1	0.317
Metformin	11 (27.5)	9 (22.5)	0.27	0.606
Other less commonly used drugs				
Antiplatelet	3 (7.5)	2 (5)	4.91	0.428
NSAID	1 (2.5)	0		
Gliptin	1 (2.5)	0		
Insulin	4 (10	3 (7.5)		

[Table/Fig-7]: Various types of drugs used by case and control group.
ACEi: Angiotensin converting enzyme; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers
Chi-square test was done. p-value <0.05 was taken as significant

DISCUSSION

A total of 40 patients with BP and 40 subjects without BP were included in the present study. Among the 80 subjects studied, most of the patients with BP and those in the comparison group belonged to the age group 56-60 years (20%). The mean age among the cases was 60.8±10.5 years and among the comparison group was 60.75±10.3 years. The female to male ratio among the cases were found to be 1.35.

The primary objective of the present study was to compare the proportion of co-morbidities among patients with BP and the comparison group of normal subjects. When, 23 (57.5%) BP patients gave history of atleast one co-morbidity before the onset of BP, only 20 (50%) normal subjects gave history of any co-morbid illness. The co-morbidities reported by BP patients in the present study were diabetes, hypertension, neurological disorders, CAD and CKD. BP was significantly associated with hypertension, diabetes mellitus, CKD, end-stage renal disease, basal cell carcinoma of the skin, and obstructive sleep apnea in a study, done by Lee S et al., [5]. In a case control study done from Germany, neurological diseases were overrepresented in BP patients compared to controls [6]. Diabetes was the most commonly observed co-morbidity, which was noted in 20 (50%) patients and a statistically significant difference between the cases and comparison group was noted. This is discordant with the findings of Askin O et al., and Pankakoski A et al., who observed hypertension as the most common co-morbidity among their patients [2,12]. The increasing prevalence of diabetes in the patients in the present study could be a reflectance of that, seen in the general population. Hypertension was the second most common 16 (40%) patients, co-morbidity noted among the patients with BP.

In recent publications, it has been emphasised that, 36%-55.8% of BP patients exhibit an increased frequency of certain neuropsychiatric disorders such as cerebrovascular occlusion, dementia, Parkinson's disease, epilepsy, schizophrenia, multiple sclerosis and immobility [5]. Teixeira V et al., and Pankakoski A et al., has reported the higher prevalence of neurological disorders among BP patients in their studies, which were 55.8% and 46%, respectively [8,12]. The cross-reaction between the common sequences of different isoforms of the 230-kDa BP antigen (BPAG1) in the skin and the neurological system plays a role in the association of BP and neurological diseases. Though, the overall reported prevalence of neurological disorders among the BP patients in the present study was only 6 (15%), patients, there was statistically significant difference between the cases and comparison group. The neurological disorders reported were CVA, parkinsoinsm and dementia. This difference from the existing literature, could be due to the difference in pattern of diseases seen in different geographical areas. The study by Jeon HW et al., also reported a lower prevalence of 11.7%, which is comparable to the findings in the present study

[13]. Exogenous triggering factors may play a role in the aetiology of autoimmune blistering diseases by regulating the immune response or by changing the antigenic properties of the epidermal basal membrane [14]. The role of exogenous triggers in pemphigoid was found at a rate of 15%-66% in previous studies. The commonly reported triggers in literature include drugs, physical factors (such as, local trauma, ultraviolet rays and radiotherapy), infections, and vaccinations [15]. In the present study, the onset of the disease was associated with a stimulating factor in 34 (85%) patients. These factors included drugs, stress, topical application, sun exposure, chemicals and trauma in the decreasing order of frequency.

A total of 10% among cases and 12.5% among comparison group were active smokers. Also, 10% of the cases and 20% of the comparison group were chronic alcoholic. However, these findings were not statistically significant. A similar study done by Akarsu S et al., has reported that, 12% of his patients with BP were both smokers and alcoholics [14]. There is no proven data till date, that suggest any risk for BP that could be triggered by alcoholism or smoking. Drug intake was the most commonly reported trigger for the onset of BP among the patients in the present study. A total of 22 (55%) patients gave a history of drug intake, prior to the onset of their illness. However, there was no statistically significant difference between the patients with BP and the comparison group. The most commonly used group of drugs by the patients were statins 15 (37.5%) patients and a statistically significant difference was noted between the cases and comparison group (p-value=0.045). This finding is similar to that observed in the Finnish cohort (33%) [12]. However, there are no documented evidence to suggest the role of statin as a trigger for BP.

The second common group of drugs noted were ACE inhibitors/ARB 14 (35%) patients and there was statistically significant difference between cases and comparison group (p-value=0.039). This is lower than that reported by Teixeira V et al., who observed that, 40.3% of his patients were using ACE inhibitors/ARB [8]. There is an impressive body of epidemiological evidence showing the association between the use of DPP-4i medication and BP. In fact, considering all drug classes, previous use of DPP-4i carries the highest risk of developing BP. The prospective study done by Lambadiari V et al., has observed that, 46% of their diabetic BP patients were using gliptins [16]. However, there was only one patient using gliptin in the present study. The lower prevalence of gliptin usage among these patients could be due to the fact that, most of the diabetic patients in this area are treated with a standard antidiabetic treatment, which mainly incudes sulfonyl ureas, metformin with/without insulin. Though, gliptins have been extensively adopted in the management of type 2 diabetes mellitus in clinical practice since, the previous decade, they have been uncommonly used by the population in this area.

Limitation(s)

Major limitation of the present study was the relatively small sample size.

CONCLUSION(S)

The BP patients are vulnerable to have many co-morbidities due to their advanced age. The most commonly observed co-morbidity among BP patients in the present study was diabetes mellitus. Since, corticosteroids, which constitute the mainstay of treatment in BP can worsen diabetes, a prompt surveillance and control of glycaemic status is needed in these patients. Various exogenous triggers have been reported by the patients, as stimulus for the initiation of the disease process and drug intake was found to be the most common trigger. Avoidance of these triggers will further help in achieving better control of the disease.

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