ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 616.529.1:616.8
DOI: 10.5937/afmnai39-35922

Original article

Neurological and Psychiatric Comorbidities in Bullous Pemphigoid

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SUMMARY

Introduction: Bullous pemphigoid (BP) is an autoimmune skin disease that typically presents with severe itching and blistering, with or without eczematous and urticarial lesions. Patients with BP are at an increased risk of comorbid conditions, especially neurologic and psychiatric diseases. Several recent studies have found a link between BP and neurological disorders, especially stroke, dementia, and Parkinson's disease. The aim of our study was to evaluate the prevalence of neurological and psychiatric comorbidities and their treatment in BP patients.
Methods: A cross-sectional, observational, descriptive study was conducted based on the analysis of the medical records of 105 patients with confirmed BP. Demographic and clinical data on BP, neurological and psychiatric comorbidities were collected and statistically analyzed for all patients.
Results: The median age was 77.8±10.6 years (range, 39-98 years). Among the study group, 71 (67,61%) patients had neurological comorbidity. Comorbidity with the highest frequency was ischemic stroke found in 28 (26,67%) patients, followed by dementia in 27 (25,71%), Alzheimer's in 11 (10,48%) and Parkinson's disease 5 (4,76%) patients. It was noted that there was a statistically significant difference among male and female patients with Alzheimer's disease (p = 0,0046) and psychiatric disorder (p = 0,044).
Conclusion: Neurological disorders usually precede the diagnosis of BP, and mortality may be higher in patients with comorbid conditions. Clinicians should be aware of the early signs and symptoms of BP, primarily in patients with primary neurological disorders such as dementia, stroke, or Parkinson's disease.

Keywords: **pemphigoid, bullous, nervous system diseases, ischemic stroke, mental disorders**

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INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune skin disease that typically presents with severe itching and blistering, with or without eczematous and urticated lesions. BP mainly affects elderly individuals, during the eight decade of life, without gender predilection. The disease is associated with an elevated risk of death compared with the general population of the same age (1).

The incidence of BP varies between 0.25 and 4.28/100.000 per year (1, 2). A study carried out in Switzerland reported an incidence of 12.1 new BP cases per million people per year, which increased up to 50 cases per million in the eighth decade of life. However, the age-standardized incidence was 6.8 new cases per million people per year, reflecting the aging of the Swiss population (3).

Studies have shown that the incidence of BP increased worldwide over the past decades. Population aging is often seen as the main contributor to an increasing prevalence of BP. Still, other factors such as exposure to drugs, improvement in clinical diagnosis, and the accuracy of laboratory techniques have also been identified as essential factors. Decreasing mortality rates among individuals with BP could contribute to the rise in the prevalence of the disease. Patients with BP are at an increased risk for comorbid conditions, such as hypertension, diabetes mellitus (DM), thromboembolism, and heart diseases (4, 5).

A study that evaluated a Finnish cohort of BP reported that the most commonly observed comorbidities were hypertension (44%), DM (34%), and ischemic heart diseases (26%) (6).

While the issue is still debated, several recent studies have found a link between BP and neurological disorders, especially stroke, dementia, and Parkinson's disease (7 - 9).

However, it has not been established what the temporal relationship between these diseases is. In addition, the association between psychiatric disorders and BP is controversial.

The mechanisms underlying this association are not clear, but an autoinflammatory reaction against BP180 or the neuronal isoform of BP230 in the human brain has been suggested. Bullous pemphigoid antigen 1 (BPAG1), also known as dystonin is a member of spectraplakin family and expressed in various tissues. BPAG1 plays crucial roles in numerous biological processes, and its neuronal isoforms are a group of large cytoskeletal linker proteins predominantly expressed in sensory neurons (10, 11).

Our study aimed to evaluate, on a cohort of consecutive patients with BP, the prevalence of neurological and psychiatric comorbidities and their treatment.

METHODS

A cross-sectional, observational, descriptive study was conducted based on the analysis of patients' medical records with confirmed BP. The study included 105 patients consecutively referred for the diagnosis and treatment of BP at the University Clinic of Dermatology in Skopje between January 1, 2015, and December 31, 2020. The diagnosis of BP was established based on typical clinical findings (blisters/erosions of the skin and/or mucous membranes, and/or erythematous-oedematous skin lesions), as well as histopathological and immunopathological criteria (12).

Data about neurological and psychiatric comorbidities of patients with confirmed BP were extracted from their electronic healthcare records (EHR) in the electronic database of the National System for Electronic Health Records. National eHealth System was introduced in the country in 2013, covering all citizens across primary, secondary, and tertiary healthcare, providing com-prehensive, institutional, and longitudinal collection of a patient's healthcare data. The EHR data are divided into two sections: administrative and med-ical content. The administrative content includes identification data (patient's complete name, medical record number, address, phone number), and lifestyle indicators (education level, profession, allergies, chronic illnesses, marital status, smoking, and alcohol consumption). Medical content includes medical reports, symptoms, physical examination results, drugs prescribed, inpatient history, and laboratory reports. The EHR contains valuable information entered by physicians and clinicians. Besides its immediate clinical use at the point of care, the EHR provides rich data that can be analyzed for clinical research (13).

Demographic and clinical data on BP, neurological and psychiatric comorbidities, including past and ongoing therapies, were collected for all patients.

The study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje and the University Clinic for Dermatology, Skopje.

STATISTICAL ANALYSIS

Data analysis was performed with the SPSS program. The mean ages of diagnoses and comorbidities overall and separately in the female and male patient groups were determined. Continuous variables were expressed as mean and range, and categorical variables as counts and percentages.

RESULTS

In the study period, a total of 105 consecutive BP patients were evaluated, of which 53 females and 52 males. The median age was 77.8 ± 10.6 years (range, 39 - 98 years), female range 39 - 98, male range 55 - 93. Among the study group, 71 (67,61%) patients have had neurological comorbidity. Comorbidity with the highest frequency was ischemic stroke reported in 28 (26,67%) cases, followed by dementia in 27 (25,71%) cases, Alzheimer's disease in 11 (10,48%) and Parkinson's disease in 5 (4,76%) cases. Additionally, 34 (32.89%) patients had a psychiatric diagnosis of the anxiety-depressive disorder, and 65 (62,5%) were prescribed chronic anxiolytic therapy. Four patients had other neurologic and psychiatric diagnoses: schizophrenia (1), myasthenia gravis (1), and epilepsy (2) (Table 1).

There was no gender difference in the extent of ischemic stroke (p = .17), dementia (p= .29) and Parkinson's disease (p = .63). The gender difference in psychiatric disorders (p = .044) and Alzheimer's disease (p = .0046) was significant in female patients being more affected. (Figure 1 a, b). For other comorbidities, there was no statistically significant difference observed.

Benzodiazepines are the most frequently prescribed drugs in treating neurological and psychiatric disorders. However, no gender differences were observed in frequency in drug prescription.

Table 1. *Gender differences in the prevalence of psychiatric and neurologic comorbidities among patients with bullous pemphigoid*

Variables	gender			p-level
	N	Male n (%)	Female n (%)	
Ischemic stroke	28 (26.67)	17 (32.69)	11 (20.75)	$X^2 = 1.9$ p = 0.17
Psychiatric disorder	34 (32.89)	12 (23.08)	22 (41.51)	$X^2 = 4.1$ *p = 0.044
Dementia	27 (25.71)	11 (21.15)	16 (30.19)	$X^2 = 1.1$ p = 0.29
Alzheimer's disease	11 (10.48)	1 (1.92)	10 (18.87)	$X^2 = 8.0$ **p = 0.0046
Parkinson's disease	5 (4.76)	3 (5.77)	2 (3.77)	$X^2 = 0.23$ p = 0.63
Psychiatric therapy	65 (62.5)	28 (53.85)	37 (71.15)	$X^2 = 3.3$ p = 0.068
Neurological therapy	44 (41.9)	24 (46.15)	20 (37.74)	$X^2 = 0.76$ p = 0.38

X2 (Pearson Chi-square); *p<0.05, **p<0.01

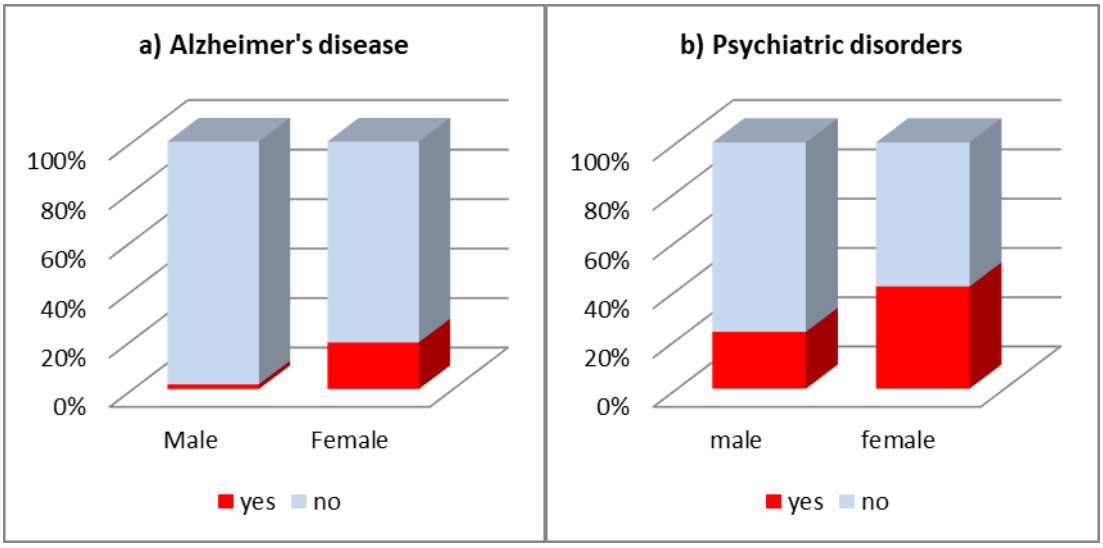

Figure 1. *Gender differences in the prevalence of a) Alzheimer's disease and b) psychiatric disorder in patients with bullous pemphigoid*

DISCUSSION

Several studies independently reported an association between BP and neurological disorders (14 - 22). The findings from this study have important implications for patient care in both dermatological and non-dermatological clinical settings.

While previous studies have reported an association between BP and neurological disorders, the specific subset differs from one investigation to another. In part, this may be due to the varying age and gender of BP patients, which has not been uniform in recent studies (14 - 22).

A possible connection could be attributed to the key proteins involved in BP pathogenesis. BPAG1 and BPAG2 are not exclusively expressed in keratinocytes. BPAG1 is divided into four isoforms: BPAG1-e (epithelial isoform), BPAG1-b (muscle isoform), BPAG1-a, and BPAG1-n (neuronal isoforms). The blood-brain barrier normally protects the neuronal isoforms BPAG-1 and BPAG-2 from infection. A blood-brain barrier problem has been linked to various neurological illnesses, allowing neuronal BP antigens to be exposed to immune cells, leading to the development of antibodies. Antibodies against epidermal isoforms can cross-react, resulting in the formation of BP. Immunoglobulins have been found not just in the BM, but also in the adjacent dermal neurons of BP patients. Drugs' roles in the development and treatment of these disorders will need to be differentiated in future research.

NEUROLOGICAL DISORDERS

A comprehensive review and meta-analysis of 14 studies comprising 23,369 patients with BP and 128,697 control participants found a substantial link between BP and neurological disorders. In comparison to the control group, people with BP had a five times higher risk of neurological diseases, three times higher risk of stroke and Parkinson's disease, four times higher risk of dementia, three times higher risk of epilepsy, and 12 times higher risk of multiple sclerosis (23).

The diagnosis of neurological illnesses frequently precedes the diagnosis of BP; the time interval varies depending on the neurological condition, but on average, it is roughly five years for all neurological diseases. According to Chen et al., 50.3 percent of patients had at least one neurological disease before being diagnosed with BP (24).

In the present study, we observed that ischemic stroke was the most prevalent neurological disorder in patients with BP (26,67%). This is partially in line with the study of Papakonstantinou et al. In their cohort, stroke was the second most common neurological disorder, observed in 9% of the patients with BP (25).

Another systematic review of 53 studies from 1984 to 2015 showed more than a 4-fold increased risk of stroke in patients with BP (26). Similarly, other studies also report stroke as one of the top

three neurological comorbidities in patients with BP (27, 28).

Distinctively from other studies, our research has shown a particularly low prevalence of other neurological disorders: dementia (25.71%), Alzheimer's disease (10.48%), and Parkinson's disease (4.76%). Per deeper research, this phenomenon could be attributed to the fact that these disorders are less diagnosed or misdiagnosed or incorrectly put in the electronic system.

PSYCHIATRIC DISORDERS

BP has been linked to various mental illnesses, including schizophrenia, unipolar and bipolar disorder, schizotypal and delusional disorders, and personality disorders. However, the risk ratios are often smaller than in neurological diseases, and the findings are inconsistent.

Both unipolar and bipolar illnesses were found to be independent risk factors for BP in a major French study (14). Teixeira et al., on the other hand, found no link between BP and depression in their investigation (20).

Patients with the psychiatric disease had a higher risk of BP, according to a Finnish national survey, notably those with schizophrenia (2.6 times), schizotypal and delusional disorders (2.1 times), and personality disorders (2.2 times). In the same study, bipolar disorder, depression, and neurotic disorders were also associated with an increased risk of BP (29).

Our study came to similar conclusions that psychiatric disorders were highly prevalent among patients with BP (32,86%), with a statistically significant difference for the women cohort. On the other hand, prescribed psychiatric therapy was not statistically different in the male and female groups.

Correspondingly, the Danish national cohort study of 6,470,450 people from 1994 to 2016 investigated the association between BP and various psychiatric disorders and the effects of medication. The results showed that multiple psychiatric disorders were associated with an increased risk of subsequent BP, regardless of psychiatric medication (4.18 times for intellectual disability, 2.32 times for substance abuse disorder, schizophrenia, 2.01 times for illness and personality disorder). This led to the conclusion that mental disorders increase the risk of developing drug-independent BP and that the drugs used to treat BP explain the development of mental disorders (30).

CONCLUSION

In summary, we found significant associations between male and female patients with BP, Alzheimer's disease and psychiatric disorders. Neurological disorders usually precede the diagnosis of BP, and mortality may be higher in patients with comorbid conditions. The number of studies assessing neurological disease among BP patients is limited and additional studies are required for definitive conclusions.

BP and psychiatric and neurological comorbidities have a complex relationship, which has a direct bearing on the management of both BP and the comorbidities. Pharmacological management of the BP can have a negative impact on psychiatric and neurological comorbidities, and vice versa. Thus, the comorbidities have to be factored into the selection of treatment modalities for BP, and the BP characteristics and treatment complications has to be considered when treating neurological conditions. Dermatologists should be able to recognize common psychiatric comorbidities in patients with BP and identify patients at risk of adverse events from high dose corticosteroid treatment.

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Article info
Received: January 17, 2022
Accepted: September 19, 2022
Online first: December 22, 2022

Neurološki i psihijatrijski komorbiditeti kod buloznog pemfigoida

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SAŽETAK

Uvod. Bulozni pemfigoid (BP) je autoimuno kožno oboljenje koje se obično javlja sa izraženim svrabom i plikovima, sa ekcemom ili bez ekcema i urtikarijom. Kod bolesnika sa BP postoji povećan rizik od komorbidnih stanja, naročito neuroloških i psihijatrijskih bolesti. U nekoliko nedavno sprovedenih studija utvrđena je veza između BP i neuroloških poremećaja, naročito moždanog udara, demencije i Parkinsonove bolesti. Cilj naše studije bila je procena prevalencije neuroloških i psihijatrijskih komorbiditeta, kao i lečenje ovih bolesti kod bolesnika sa BP.
Metode. Opservaciona, deskriptivna studija preseka sprovedena je na osnovu analize medicinskih kartona 105 bolesnika sa potvrđenom dijagnozom BP. Za sve bolesnike sakupljeni su i statistički analizirani svi demografski i klinički podaci o BP i neurološkim i psihijatrijskim komorbiditetima.
Rezultati. Srednja vrednost godina iznosila je 77,8 ± 10,6 godina (opseg, 39 – 98 godina). Kod ispitivane grupe, 71 (67,61%) bolesnik imao je neurološke komorbiditete. Komorbiditet sa najvećom učestalošću bio je ishemijski moždani udar kod 28 (26,67%) bolesnika, praćen demencijom kod 27 (25,71%) bolesnika, Alchajmerovom bolešću kod 11 (10,48%) bolesnika i Parkinsonovom bolešću kod 5 (4,76%) bolesnika. Zabeležena je statistički značajna razlika između bolesnika muškog i ženskog pola sa Alchajmerovom bolešću (p = 0,0046) i psihijatrijskim poremećajima (p = 0,044).
Zaključak. Neurološki poremećaji obično prethode dijagnozi BP i mortalitet može biti veći kod bolesnika sa komorbidnim stanjima. Kliničari bi trebalo da obrate pažnju na rane znake i simptome BP, prvenstveno kod bolesnika sa primarnim neurološkim poremećajima, poput demencije, moždanog udara ili Parkinsonove bolesti.

Ključne reči: **pemfigoid, bulozni, bolesti nervnog sistema, moždani udar, mentalni poremećaji**