Bullous pemphigoid and neurological disease: statistics from a dermatology service*

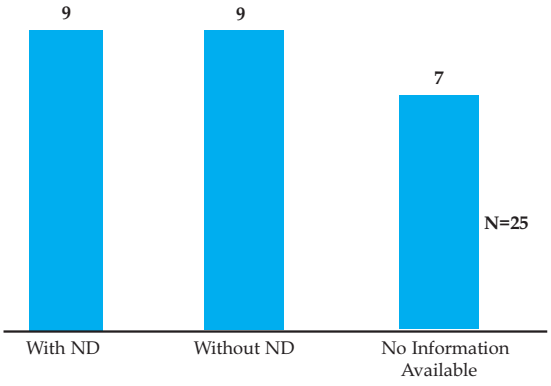
Monica Jidid Mateus Tarazona[1]
Amanda Nascimento Cavalleiro de Macedo Mota[1]
Alexandre Carlos Gripp[1]
Natasha Unterstell[1]
Aline Lopes Bressan[1]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20153334

Abstract: Bullous pemphigoid (BP) is an autoimmune, acquired, cutaneous disease caused by the production of autoantibodies against hemidesmosomes' components in the basement membrane. The estimated incidence in Europe ranges from 7 to 43 cases per million inhabitants per year. Several studies have reported an association between BP and neurological disorders (ND). Our cohort of Bullous pemphigoid and ND is the first in Brazil and showed a significantly high prevalence of neurological and/or psychiatric diseases, especially cerebrovascular accident (CVA) and dementia, in agreement with the prevalence reported in several studies published in the medical literature in recent years.
Keywords: Dementia; Pemphigoid, bullous; Stroke

A retrospective chart review was performed comprising all patients with clinical and/or histopathological diagnosis of BP treated at the Dermatology Department of Pedro Ernesto University Hospital in Rio de Janeiro, Brazil from 2006 to 2012. Next, those with histopathological confirmation of BP were selected (Graph 1). Records of 40 patients were analyzed, 15 of which were excluded for not having conclusive histopathological data on BP. The average age of patients was 73.9 years, ranging from 38 to 92 years and regarding gender, 18 women (72%) and 7 men (28%) (Chart 1) were studied. The age range of patients who showed the highest association of BP and ND was between 80 and 89 years (Graph 2 and 3). Of the 25 patients with histopathologically confirmed BP, 9 (36%) had clinical diagnosis of at least one neurological or psychiatric disorder and 9 (36%) did not have associated neurological diseases. In 7 cases (28%), no record that could confirm or rule out the investigated pathologies was found. Associated neurological diseases in these cases were: cerebrovascular accident (CVA) or stroke (44.4%), dementia (22.2%), panic disorder syndrome (11.1%), depression (11.1%) and epilepsy (11.1%) (Graph 4). One patient had two associated diseases, stroke and migraine, and one patient had a history of two episodes of stroke prior to the diagnosis of BP.

Bullous pemphigoid is the most common bullous disease.[1,2,3] It has a bimodal distribution, predominating in elders, although it may also affect small children. Clinically it is characterized by papular, urticariform, pruritic lesions, that progress to tense bullae on erythematous or normal skin, most fre-



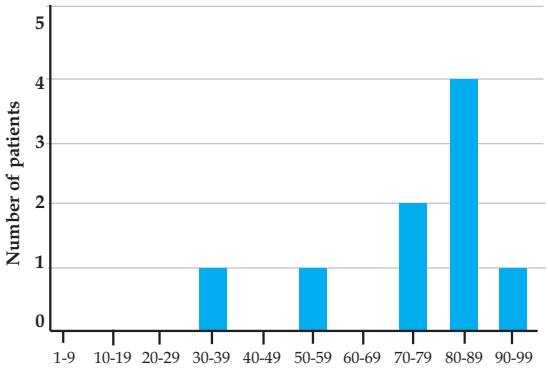
Graph 1: patients diagnosed with BP 2007-2012 Dermatology Service at Pedro Ernesto University Hospital

Received on 20.12.2013.
Approved by the Advisory Board and accepted for publication on 02.06.2014.
* Work performed at Pedro Ernesto University Hospital - Rio de Janeiro State University (HUPE-UERJ) – Rio de Janeiro (RJ), Brazil.
Conflict of interest: None
Financial Support: None

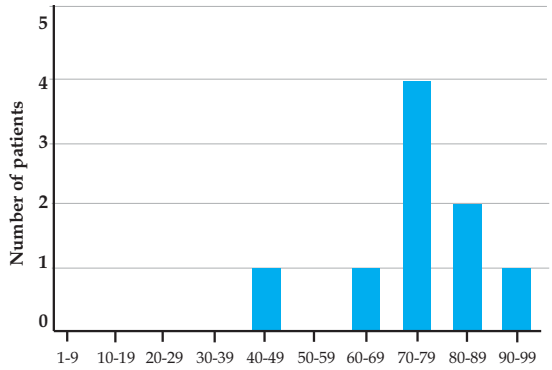
[1] Universidade do Estado do Rio de Janeiro (UERJ) – Rio de Janeiro (RJ), Brazil.

Chart 1: Clinical data of patients with bullous pemphigoid and neurological disease

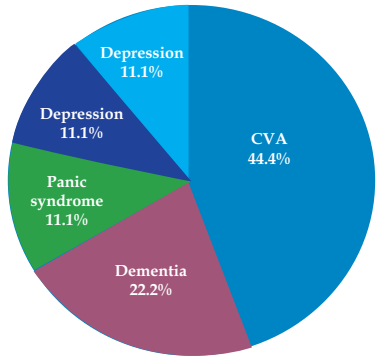
Patient No	Gender	Age at BP diagnosis (years)	Presence of ND	Type of ND
1	M	71	No	NA
2	F	55	Yes	CVA
3	F	77	NIA	NA
4	F	75	NIA	NA
5	F	73	No	NA
6	F	88	No	NA
7	F	87	Yes	CVA
8	M	88	Yes	CVA
9	F	83	Yes	Epilepsy
10	F	73	No	NA
11	M	50	NIA	NA
12	F	71	No	NA
13	M	38	Yes	Panic syndrome
14	F	85	No	NA
15	F	77	Yes	Dementia
16	M	88	NIA	NA
17	F	47	No	NA
18	F	75	NIA	NA
19	F	86	Yes	Depression
20	F	91	Yes	Dementia
21	F	82	NIA	NA
22	F	63	No	NA
23	M	92	No	NA
24	F	64	NIA	NA
25	M	70	Yes	CVA



Graph 2: age histogram of patients with BP and ND



Graph 3: age histogram of patients with BP without ND



Graph 4: age histogram of patients with BP without ND

quently in the flexures and abdomen.[3,4] Histopathologic examination shows subepidermal blisters, and in some cases, eosinophilic spongiosis, particularly in the initial plaques.[5]

Dementia, stroke, multiple sclerosis, epilepsy, Parkinson's disease, Shy-Drager syndrome and amyotrophic lateral sclerosis are the neurological diseases most frequently associated with BP.[1,2,6,7,8] The pathophysiologic mechanism of this association is not completely understood. It is likely that BP antigens, such as BPA1 and BPA2, act as autoreactive antigens in the brain and skin.[6] Studies have detected circulating and reactive antibodies against human brain antigens in the sera of patients with BP and neurological disease, which would be linked to the development of cutaneous disease.[2,6] A recent study demonstrated that the genetic alteration of BPA1's neuronal isoform in mice led to neurological degeneration and dystonia, secondary to the accumulation of intermediate filaments in motor neurons. It was suggested that this accumulation could induce the loss of tolerance to BPA1's neuronal isoform, possibly inducing a cross-reaction with the epidermal isoform.[2] There are three main forms of BPA1. The neural isoform BPA1-a, expressed in the brain and the muscle isoform BPA1-b detected in the heart.[6,7] The skin is the exclusive site of BPA1-e isoform's expression, although the other two forms have also been found in low levels in that location, which enables the cross-reactivity phenomenon. BPA1 and BPA2 are located in the synaptic and extrasynaptic regions of the central nervous system (CNS), being part of the anchoring complex that stabilizes the neural terminations to the extracellular matrix, similarly to BPA1 and BPA2 in the cutaneous dermoepidermal junction.[6] It is suggested that CNS alterations in the

course of neurological diseases and/or blood-brain barrier changes, may expose the neuronal isoform of BPA1/BPA2 leading to autoimmune response and cross-reaction with cutaneous antigens, resulting in the development of BP.[6,7] This would explain why, in general, the neurological disease precedes the development of BP in variable lengths of time.[7]

Several studies have reported high prevalence of neurological disorders in patients with BP compared with control groups.[4,6,7,9] Our data also demonstrated the high prevalence of neurological disorders in patients diagnosed with BP (36%). Although bullous pemphigoid is not overtly prevalent in any race or sex, most of our cases were diagnosed in women (72%) and they were the ones with a more frequent association of BP and neurologic disease (77%).[3,4] The majority of patients diagnosed with BP were in the age group of 70-79 years (36%), and 19 patients (76%) had more than 69 years, concurring with previously published data. Cordell *et al* published a study with 341 patients, in which the neurological diseases most often associated were dementia in 20% of cases, followed by stroke (15%). Conversely, Chen *et al* in a study with 3,485 patients found stroke as the most prevalent disease with 1,284 cases, followed by dementia (617 cases), Parkinson's disease (416 cases), epilepsy (201 patients) and schizophrenia (22 cases). Associated inflammatory diseases such as psoriasis (74 cases) and rheumatoid arthritis (20 cases) were also detected. Our results coincide with the latter study, in finding stroke as the most frequently associated neurological disease, followed by dementia, epilepsy, depression and panic disorder syndrome.

In summary, our study of BP and ND is the first one presented in Brazil and it demonstrates a significantly higher prevalence of neurological disorders, especially stroke and dementia, associated with BP in agreement with the results reported in several papers published in the medical literature in recent years.❑

REFERENCES

1. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V, Wojnarowska F. The association of bullous pemphigoid with cerebrovascular disease and dementia: a case control study. Arch Dermatol. 2010;146:1251-4.
2. Cordel N, Chosidow O, Hellot MF, Delaporte E, Lok C, Vaillant L, et al. Neurological disorders in patients with bullous pemphigoid. Dermatology. 2007;215:187-91.
3. Lo Schiavo A, Ruocco E, Brancaccio G, Caccavale S, Ruocco V, Wolf R. Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. Clin Dermatol. 2013;31:391-9.
4. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013;263:320-32.
5. Rapini RP. Practical Dermatopathology, 2nd ed. Elsevier; 2012.
6. Chen J, Li L, Chen J, Zeng Y, Xu H, Song Y, et al. Sera of elderly bullous pemphigoid patients with associated neurological diseases recognize bullous pemphigoid antigens in the human brain. Gerontology. 2011;57:211-6.
7. Seppänen A. Collagen XVII: a shared antigen in neurodermatological interactions? Clin Dev Immunol. 2013;2013:240570.
8. Lloyd-Lavery A, Chi CC, Wojnarowska F, Taghipour K. The associations between bullous pemphigoid and drug use: a UK case control study. JAMA Dermatol. 2013;149:58-62.
9. Foureur N, Descamps V, Lebrun-Vignes B, Picard-Dahan C, Grossin M, Belaich S, et al. Bullous pemphigoid in a leg affected with hemiparesia: a possible relation of neurological diseases with bullous pemphigoid? Eur J Dermatol. 2001;11:230-3.
10. Chen YJ, Wu CY, Lin MW, Chen TJ, Liao KK, Chen YC, et al. Comorbidity profiles among patients with bullous pemphigoid: a nation wide population based study. Br J Dermatol. 2011;165:593-9.

MAILING ADDRESS:
Monica Jidid Mateus Tarazona
Boulevard 28 de setembro, 77
Vila Isabel
20551-030 - Rio de Janeiro - RJ
Brazil
E-mail: monicajmateus@hotmail.com

How to cite this article: Tarazona MJM, Unterstell N, Mota A, Bressan A, Gripp A. Bullous pemphigoid and neurological disease: statistics from a dermatology service. An Bras Dermatol. 2015;90(2):280-2.