Involvement of neuropeptides in pruritus of patients with bullous pemphigoid: A pilot study

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Involvement of neuropeptides in pruritus of patients with bullous pemphigoid: A pilot study

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ABBREVIATION

BP: bullous pemphigoid

CGRP: calcitonin gene-related peptide

CRCP: CGRP receptor component

NK-1R: neurokinin-1 receptor

SP: substance P

KEY WORDS

bullous pemphigoid

calcitonin gene-related peptide

neurokinin-1 receptor

pruritus

neuropeptide

To the Editor,

Bullous pemphigoid (BP) is an autoimmune blistering disease, characterized by tense blisters and erythematous urticated plaques on the skin. The disease mainly affects the elderly and usually leads to intense itchy sensation.[1] Pruritus in BP is resulted from the mediators released by innate immunity cells, such as mast cells and eosinophils, and from the Th2 cytokines, which have been shown markedly elevated in patients with BP.[2] Pruritus in most of BP patients can be relieved by medical treatments. However, in certain patients, the intensity of pruritus is high and could not be satisfactorily reduced by systemic anti-histamines and even immunomodulatory drugs.

In order to further explore other possible mediators of pruritus in BP patients, we performed a retrospective study to collect the data of BP patients with different degrees of pruritus. The study was approved by the research ethics committee (IRB: NTUHREC 201006012R) and the informed consents were obtained from all the participants. The diagnosis of BP was confirmed based on the typical clinical and histological presentations, and positive findings in direct and indirect immunofluorescence studies. Fifteen BP patients, including 8 females and 7 males, were recruited with an average age of 70 (Table 1). Among them, 6 patients had intractable pruritus which could not be relieved by high dose of systemic anti-histamines and corticosteroids, while other 9 patients presented with tolerable pruritus.

The baseline levels of serum BP auto-antibodies between the two groups did not show significant differences (Mann-Whitney U test, Pvalue = 0.380 and 0.898 in anti-BP180 IgG and IgE; P value = 0.661 and 0.093 in anti-BP230 IgG and IgE). The amount of tissue mast cells in specimens of skin biopsies were also similar between the groups (Chi-square test, P value = 0.912). We performed immunohistochemistry stains to investigate the expressions of substance P (SP) (, 13839-1-AP), neurokinin-1 receptor (NK-1R) (Novus Biologicals, , NB100-74469), calcitonin gene-related peptide (CGRP) (, 250602), and CGRP receptor component (CRCP) (, ab139264) in skin specimens of these patients (Figure 1). The intensity of IHC stains were classified based on the area of staining occupying the high power field (HPF): none, 0 point; $< 1/3$: 1 point; $1/3$ [?] but $< 2/3$, 2 points; $2/3$ [?], 3 points. BP patients with intractable pruritus showed significant higher expressions of NK-1R and CGRP comparing to those with tolerable pruritus (Chi-square test, P value = 0.011 and 0.020, respectively). (Figure 1)

The role of neuropeptides in the formation of pruritus has been demonstrated in several skin diseases, such as atopic dermatitis[3] and psoriasis.[4] The involvement of SP and NK-1R in the pruritus of BP patients has also reported in one previous study.[5] It shows that most cells expressing NK-1R in BP patients are eosinophils. In line with this previous observation, in addition to SP/NK-1R axis, the results of our study showed that the presence of both NK-1R and CGRP containing nerve endings in the skin contribute to the intractable pruritus in BP patients. Other than pruritus, these neuropeptides can also evoke neurogenic inflammation,[6] resulting in erythema and edema, contributing to the formation of these characteristic presentations of BP patients. These findings may help the clinicians trying new therapeutic approaches when treating BP patients with intractable pruritus. However, our study has some limitations, such as a small sample size, a lack of control group, and a retrospective study design. A larger prospective study involving a control group is needed to confirm our results.

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Table 1 Demographics of patients with bullous pemphigoid

	Age	Gender	Pruritus	BP180* IgG	BP180* IgE	BP230* IgG	BP230* IgE	Intensity of IHC stains Mast cells	Intensity o SP
1	58	F	T	14.5	0.3914	43	0.4648	1	1
2	75	M	I	81.2	0.433	4.5	0.5526	2	1
3	70	M	I	136.7	0.4428	88	0.7104	2	3
4	30	M	T	60.2	0.4063	2.4	0.5525	2	1
5	79	F	I	89.4	0.3985	34.3	0.5918	3	2
6	71	M	I	10.7	0.3416	53.5	0.4992	2	1
7	88	F	T	114.6	0.3104	4	0.3153	2	1
8	59	F	T	68.8	0.4013	2.2	0.2957	2	2
9	82	M	I	NA	0.2724	NA	0.5533	1	3
10	83	F	T	107	0.3356	2.7	0.225	3	2
11	51	F	I	84.2	0.1449	1.3	0.247	2	2
12	79	F	T	35	0.1905	58.3	0.561	2	2
13	90	M	T	14.4	0.1759	112.1	0.4944	2	1
14	78	F	T	63.4	0.4661	4.1	0.4321	3	1
15	62	M	T	NA	NA	NA	NA	1	2

CGRP: calcitonin gene-related peptide, CRCP: CGRP receptor component, F: female, I: intractable, IHC: immunohistochemistry, M: male, NA: non-available, NK-1R: neurokinin-1 receptor, SP: substance P, T: tolerable

* The levels of IgG antibody were measured in IU/ml as the manufacturer's protocol, while those of IgE antibody were measured in O.D. values.

FIGURE LEGEND

Figure 1. Immunohistochemistry stains of SP, CGRP, and their receptors. Representative pictures (200X) are shown. Comparisons between the groups are using chi-square tests.