334

Liu H T[1], Lin H[2], Kuo H C[3]

1. *Buddhist Tzu Chi General Hospital, Hualien, Taiwan ; Institute of Pharmacology and Toxicology, Tzu Chi University, Hualien, Taiwan,* ***2.*** *Institute of Pharmacology and Toxicology, Tzu Chi University, Hualien, Taiwan,* ***3.*** *Buddhist Tzu Chi General Hospital, Huailen, Taiwan*

CHRONIC INFLAMMATION BUT NOT UROTHELIUM DYSFUNCTION IN PATIENTS WITH OVERACTIVE BLADDER SYNDROME

Hypothesis / aims of study

Recent investigations have linked overactive bladder syndrome (OAB) with chronic inflammation. Urinary nerve growth factor, cytokines and serum C-reactive protein have been demonstrated to increase in patients with OAB and interstitial cystitis/ painful bladder syndrome (IC/PBS). Previous reports have suggested that IC/PBS is associated with increased activated mast cell numbers in the bladder and disruption of the barrier function of the urothelium. However, there is no study investigating the mast cell activation and urothelium barrier dysfunction in OAB. Since there are similarities in the inflammatory protein expression between OAB and IC/PBS, therefore, in this study the Infiltration of mast cells and the distribution of protein involved in barrier function were explored by immunohistochemical assessment of E-cadherin and ZO-1 in the bladder tissue of patients with OAB and IC/PBS.

Study design, materials and methods

Bladder wall biopsies were performed in 27 patients with OAB, 18 patients with IC/PBS, and 19 patients with stress urinary incontinence but without urgency frequency symptoms and served as controls. The expression of junction protein E-cadherin, tight junction protein ZO-1 and activated mast cell in bladder wall from these patients were evaluated quantitatively using immunofluorescence staining. The percentages of tryptase-positive mast cells were calculated from 5 consecutive high-power fields (X400) in the area with the highest dense infiltrate. Confocal microscopy was used to capture ZO-1 image. Density of E-cadherin and ZO-1 expression were quantified with Image J software. Two to three sections per sample from OAB or IC/PBS bladders and controls were examined. Statistical analysis was performed using one-way ANOVA and p value small than 0.05 was considered as significance. This study was approved by the Institution Review Board of the hospital.

Results

The OAB group consisted of 6 women and 21 men aged from 42 to 85 years old (mean 72). Patients with IC/PBS were 16 women and 2 men aged 21 to 72 years old (mean 42). Control patients were 19 women aged 29 to 71 years old (mean 54). All OAB patients presented with urgency and urgency incontinence (OAB wet) and the bladder tissue were obtained during procedure of intravesical botulinum toxin injection. All patients with IC/PBS had been proven by cystoscopic hydrodistention and had characteristic glomerulation. The bladder tissues of the controls were obtained during anti-incontinence surgery. The number of mast cells in suburothelium and detrusor area was low in the control group (mean ± standard error 1.77 ± 0.47, range 0.00-9.00). But a highly significant increase of the mast cells infiltration was observed in the specimens from IC/PBS (4.64 ± 0.72, range 1.00-10.00)and OAB patients (4.00 ± 0.55, range 0.00-11.00) (p=0.008 and p=0.024, respectively). The expression level of E-cadherin and ZO-1 in the IC/PBS bladder (mean ± standard error 59.05 ± 9.48 and 7.45 ± 0.99) were significantly down regulated compared with that in the control group (96.30 ± 9.15 and 14.55±2.08 ; p=0.009 and p=0.013). However, compare the density of E-cadherin and ZO-1 between control bladder and OAB patients (79.41 ± 6.90 and 13.46 ± 1.32), there were no significant difference between the two group (p=0.334 and p=0.876). (Table1, figure 1) These results suggest that the pathophysiology of IC/PBS and OAB both might linked with chronic inflammation. However, IC/PBS is associated with impairment of the barrier function of the urothelium but the bladder urothelium barrier in OAB is not disrupted.

Interpretation of results

In our study, patients with OAB and IC/PBS all had significantly greater number of mast cells in the bladder wall compared with controls. The bladder biopsies from IC/PBS patients reported previously have confirmed the involvement and presence of mast cells in the detrusor. Mast cells have been considered as crucial effector cells for the immune response implicated in the pathogenesis of IC/PBS. Bladder mast cell activation has been reported as a characteristic pathological finding in a subset of IC/PBS patients. Measurement of surrogate mast cell-related products in urine has been previously studied to assess the disease extent in patients. Since patients with OAB and IC/PBS all had elevated mast cell activities compared with that of the controls in this study, It is possible that a common pathway of chronic inflammation exists in the pathogenesis between these two diseases.

Concluding message

The results of this study suggest that both IC/PBS and OAB are associated with chronic inflammation and the role of bladder tissue mast cells in the pathogenesis and pathophysiology of OAB and IC/PBS is worthy of further investigation.

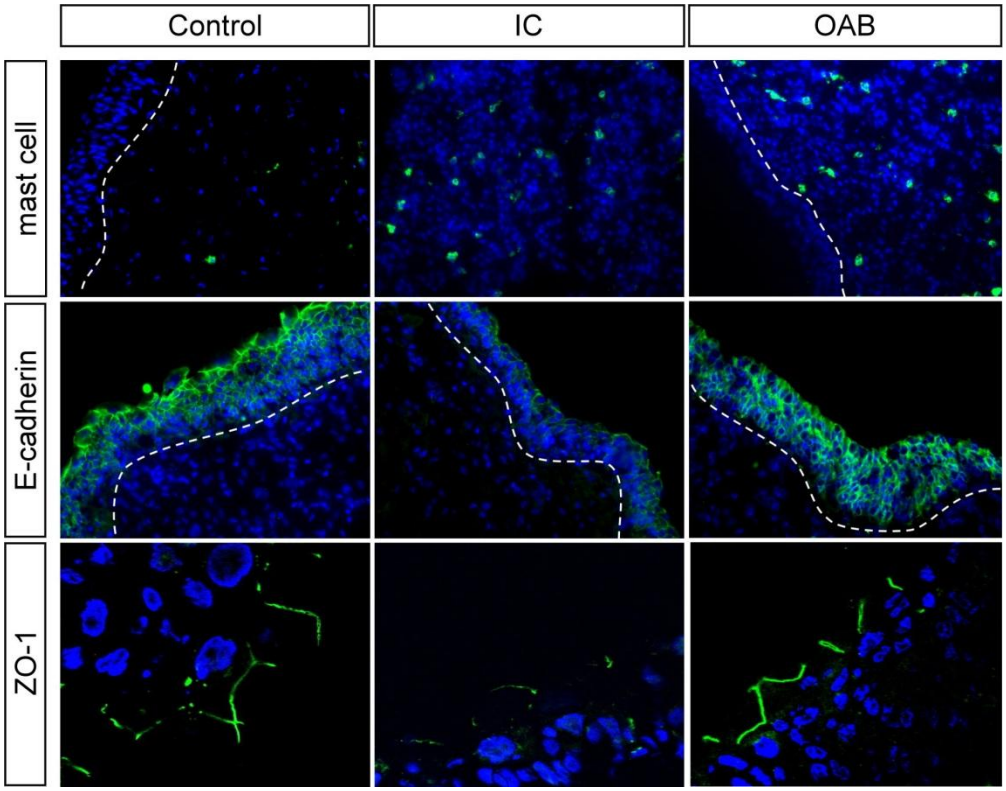
Table 1. Expression level of mast cell, E-cadherin and ZO-1 protein in bladder tissue of OAB and IC/PBS patients

	Control n=19	**IC n=18**	**OAB n=27**	**Control vs IC Control vs OAB OAB vs IC**
Age	53.63±11.88 29~71	41.78±13.48 21~72	71.63±10.77 42~85	
Gender	F: 19	F: 16 M: 2	F: 6 M: 21	
Mast cells	1.77±0.47 0.00~9.00	4.64±0.72 1.00~10.00	4.00±0.55 0.00~11.00	P=0.008** P=0.026* P=0.740

E-cadherin	96.30±9.15 44.83~166.24	59.05±9.48 7.5~155.56	79.41±6.90 17.50~150.25	P=0.009** P=0.334 P=0.143
ZO-1	14.55±2.08 2.19~37.69	7.45±0.99 1.44~14.05	13.46±1.32 5.17~27.79	P=0.013* P=0.876 P=0.024*

*: p<0.05; **: p< 0.01

Figure 1. Immunofluorescence staining of mast cell activity, E-cadherin and ZO-1 in OAB, IC/PBS and control bladder



Specify source of funding or grant	**None**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Research Ethics Committee of Buddhist Tzu Chi General Hospital**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**