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CHANGES OF SUBUROTHELIAL INFLAMMATION AND JUNCTION PROTEIN E-CADHERIN IN CHRONIC SPINAL CORD INJURED BLADDERS AFTER DETRUSOR BOTULINUM TOXIN A INJECTIONS

Hypothesis / aims of study

Neurogenic detrusor overactivity (NDO) is a consequence of the change in bladder reflex pathways in chronic spinal cord injured (SCI) patients. Patients with neurogenic voiding dysfunction (NVD) caused by SCI were vulnerable to chronic cystitis, inflammation, or chronic bacterial infections. It probably is related to the abnormalities of bladder urothelium. The urothelium plays a role in modulating bladder sensory nerve ending excitability. Urothelial dysfunction has been observed and thought to be involved in the pathogenesis in several urinary bladder diseases. Botulinum toxin A (BoNT-A) has been demonstrated effective in treatment of NDO in SCI patients, and an anti-inflammatory effect has been noted in treating overactive bladder and interstitial cystitis. This study was aimed to investigate the differences of urothelial junctional protein and suburothelial inflammation between patients with chronic SCI and normal controls and the changes of urothelial dysfunction after detrusor BoNT-A injections in SCI bladders.

Study design, materials and methods

A total of 24 patients with chronic suprasacral SCI and refractory NDO proved by videourodynamic study were enrolled. Another 20 patients with stress urinary incontinence served as the control group. The urothelium were assessed by cold-cup biopsy at baseline, 3 months and 6 months after detrusor BoNT-A 200U injections for SCI patients. Bladder biopsy was only performed at baseline in control group. Immunofluorescence (IF) staining of adhesive protein E-cadherin and tryptase (indicating mast cell activation) were performed. The fluorescence intensity of E-cadherin was measured using an Image J method. The percentage of activated mast cells were measured and quantified as positive cell per area unit (4 μm^2). The differences of E-cadherin expression in the urothelium and activated mast cell numbers in the suburothelium were compared between SCI patients and controls at baseline, and between baseline, 3 months and 6 months after BoNT-A injection in SCI patients.

Results

IF results showed no significant difference in the distribution of E-cadherin expression at 6 months after BoNT-A injection in bladder tissue of SCI patients compared with the baseline (36.40 ± 19.70 v 34.74 ± 18.08, p=0.886). The tryptase signal also showed no significant difference between baseline and 6 months after BoNT-A injection (13.19 ± 3.82 v 11.72 ± 6.89, p=0.493). The E-cadherin expression was 40.95 ± 23.53 and mast cell count was 5.06 ± 6.08 in the controls, all showed significantly different from that in the SCI patients (Table 1) (Fig.1). In the subgroup of different injury levels, the result still showed no significant differences (Table 2). Although the results did not reveal significant difference between baseline and 6 months after BoNT-A injection in SCI patients, we could find a trend that the junction protein slightly improved and the mast cell count slightly decreased at 3 months after BoNT-A injection. These changes in E-cadhein expression and mast cell activation at 3 and 6 months in SCI patients showed a similar trend with the resolution of detrusor overactivity and urinary incontinence.

Interpretation of results

The bladder of chronic SCI had a decreased expression of E-cadherin in urothelium, and increased activated mast cell numbers. The disruption of the urothelial barrier may initiate a cascade of events of bladder dysfunction, leading to suburothelium inflammation and then the vulnerability of chronic or recurrent cystitis/ infection. The suburothelial inflammation might also affect urothelial function, forming a vicious cycle. Detrusor BoNT-A injection can decrease detrusor overactivity and also has an anti-inflammatory effect on resolution of suburothelail inflammation as well as restoration of the junction protein concentration. However, this effect would decrease as time goes by. At 6 months after the BoNT-A injection, the inflammation and junction protein deficiency would relapse, suggesting the neurogenic inflammation due to SCI could not be adequately relieved after single BoNT-A injection.

Concluding message

This is the first study to assess the effect of BoNT-A on the urothelial dysfunction in SCI patients. The preliminary results suggest urothelial barrier might be impaired and suburothelial inflammation increased in chronic SCI patients. These urothelial dysfunction might be recovered after BoNT-A injection.

Table 1. Expression of E-cadherin, mast cell activation in controls and patients with chronic SCI bladders at baseline and 6 months after BoNT-A treatment.

Target	Control (n=20)	Baseline (n=24)	6 M after BoNT-A (n=24)	P value*
E-cadherin	40.95±23.53	34.74±18.08	36.40± 19.70	P=0.886
Activated mast cell	5.06± 6.08	11.72± 6.89	13.19 ± 3.82	P=0.493

*Comparison between baseline and 6 months after BoNT-A in SCI Patients

Table 2. Expression of E-cadherin, mast cell activation in patients with chronic SCI bladders of different injury level at baseline and 6 months after BoNT-A treatment.

Injury Level	Target	Baseline	6 M after BoNT-A	P value
C-spine injury	E-cadherin	33.23 ± 22.17	38.12 ± 20.66	P=0.256

(N=10)	Activated mast cell	12.17 ± 6.30	11.93 ± 3.45	P=0.799
T-spine injury (N=13)	E-cadherin	35.09 ± 18.08	33.75 ± 19.71	P=0.600
	Activated mast cell	12.14 ± 7.33	14.18 ± 4.09	P=0.552
L-spine injury (N=1)	E-cadherin	44.34	53.73	
	Activated mast cell	2.43	12.99	

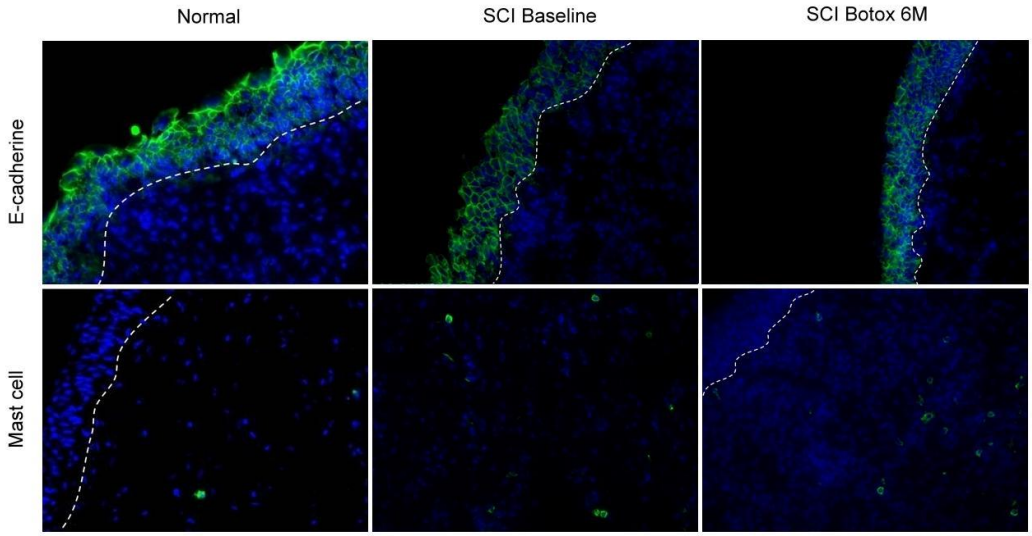

Fig.1. The expression of E-cadherin and mast cell activities in the controls and SCI patients at baseline and 6 months after BoNT-A injection

Disclosures
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