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UROTHELAIL DYSFUNCTION AND CHRONIC INFLAMMATION IN PATIENTS WITH SPINAL CORD INJURY OF DIFFERENT INJURY LEVEL AND CORRELATION WITH URODYNAMICS FINDINGS

Hypothesis / aims of study

Urothelial dysfunction were observed and thought to be involved in the pathogenesis in several urinary bladder diseases. Patients with neurogenic voiding dysfunction (NVD) caused by spinal cord injury (SCI) were vulnerable to chronic cystitis, inflammation, or chronic bacterial infections. It probably is related to the abnormalities of bladder urothelium. This study is aimed to investigate the differences of urothelial junctional protein and suburothelial inflammation between patients with chronic SCI of different injury levels and normal control. We also correlated them with the clinical urodynamic findings.

Study design, materials and methods

Bladder wall biopsies were performed in 34 chronic SCI patients with complete injury, and 20 normal controls. Immunofluorescence (IF) staining of junction protein E-cadherin, tryptase (indicating mast cell activation), and TUNEL (indicating urothelial apoptosis) 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 urothelium and activated mast cell / apoptotic cell numbers in suburothelium were compared between patients with chronic SCI of different injury levels and normal controls. The parameters in video-urodynamic study (VUDS) were also analyzed.

Results

The mean interval from the episode of SCI and bladder biopsies was 9.3 ± 8.4 years (range from 1.5 to 33.4). In IF staining, decreased distribution of E-cadherin (20.9 ± 14.1 VS 50.1 ± 21.3), increased activated mast cell infiltration (16.6 ± 6.9 VS 1.9 ± 2.0) and elevated apoptotic cells in suburothelium (2.5 ± 1.1 VS 0.1 ± 0.3) were examined in chronic SCI patients compared with controls (Table 1) (all $p<0.01$). Between 15 C-SCI and 19 T-SCI patients, the mean age was 37.9 ± 11.8 years with similar intervals. There was no significant difference in E-cadherin expression in urothelium, activated mast cell numbers in suburothelium, or suburothelial apoptosis between C-SCI and T-SCI patients. In VUDS, C-SCI and T-SCI patients had similar cystometric bladder capacity (CBC), detrusor voiding pressure (Pdet), maximal urinary flow rate (Qmax), and post-void residual volume (PVR). The quality of life (QoL) scores between these two groups were also similar. Activated mast cell numbers were negatively related to the expression of E-cadherin in urothelium (R^2= 0.321. $p=0.001$) (Fig. 1A). OoL scores were also negatively related to Pdet (R^2= 0.216. $p<0.001$) (Fig.1B).

Interpretation of results

The bladder of chronic SCI had a decreased expression of E-cadherin in urothelium, and increased activated mast cell and apoptotic cell numbers. Activated mast cell numbers were negatively related to the expression of E-cadherin. It presented with a dysfunctional urothelium and an inflammatory bladder, which were related significantly. The disruption of the urothelial barrier may initiate a cascade of events of bladder, 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. C-SCI and T-SCI patients had the similar findings in the immunohisochemistry analysis and VUDS, implying the similar pathophysiology and clinical picture of NVD. The negative correlation of QoL scores and Pdet was probably due to the impact of urinary incontinence, especially in these chronic SCI patients with complete injury.

Concluding message

The decreased E-cadherin expression accompanied with increased mast cell infiltration and increased suburothelial apoptosis in chronic SCI bladders. Urothelial dysfunction probably accounted for the bladder of chronic SCI being vulnerable to chronic cystitis, inflammation, or bacterial infection. C-SCI and T-SCI patients had the similar findings in the immunohisochemistry analysis of bladder and VUDS. QoL scores in chronic SCI were negatively related to Pdet.

Table 1. The demographics, immunoflurescent analysis of bladder tissue, and VUDS in normal controls and chronic SCI patients.

	Control	Cervical SCI	Thoracic SCI	Total SCI	P value #
Number	20	15	19	34	
Interval (year)		7.4 ± 7.0	10.5 ± 9.0	9.3 ± 8.4	0.332
Age	53.5 ± 11.5	40.5 ± 14.3	35.9 ± 9.4	37.9 ± 11.8	0.263
E-cadherin	50.1 ± 21.3	19.5 ± 12.2	22.0 ± 15.6	20.9 ± 14.1*	0.617
Activated Mast cell numbers	1.9 ± 2.0	15.3 ± 5.5	17.6 ± 7.8	16.6 ± 6.9*	0.330
Apoptotic cell numbers	0.1 ± 0.3	2.4 ± 1.0	2.7 ± 1.2	2.5 ± 1.1*	0.771
VUDS					
CBC (mL)		255.8 ± 153.7	239.47 ± 168.2	246.1 ± 160.1	0.783
Pdet (cmH_2O)		28.9 ± 17.9	44.5 ± 25.1	38.2 ± 23.5	0.064

Qmax (mL/sec)		4.5 ± 5.6	4.5 ± 5.6	4.5 ± 5.6	0.975
PVR (mL)		180.7 ± 114.2	169.5 ± 113.9	174.2 ± 112.4	0.781
QoL		3.75 ± 1.06	3.79 ± 1.44	3.77 ± 1.28	0.935

*: p< 0.01, total SCI patients were compared with controls
#: p value between C-SCI and T-SCI patients
CBC: cystometric bladder capacity; Pdet: detrusor voiding pressure; Qmax: maximal urinary flow rate (Qmax); PVR: post-void residual volume; QoL: quality of life

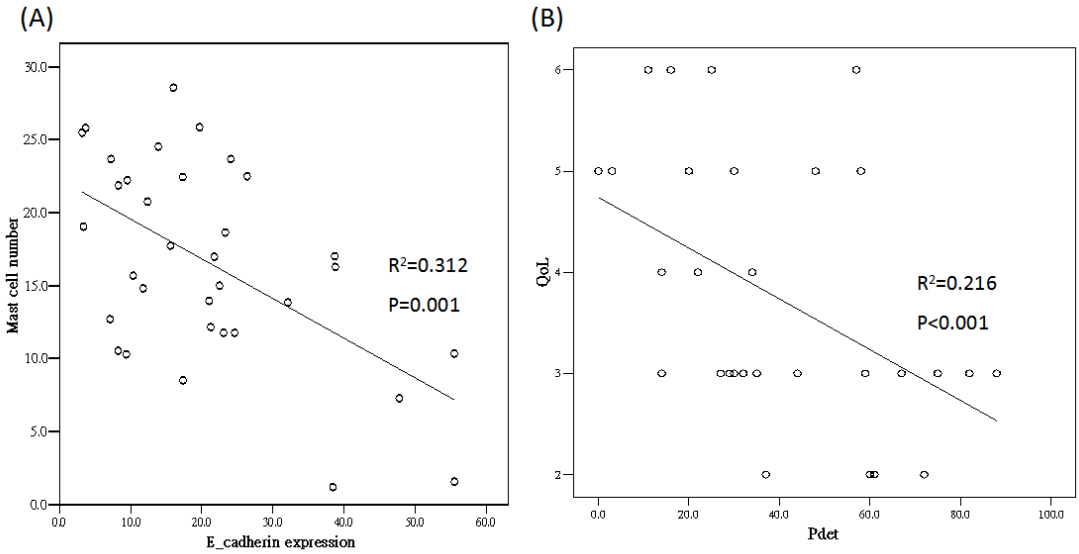

Fig. 1. (A) The correlation of E-cadherin expression in urothelium and activated mast cell numbers in suburothelium. (B) The correlation of Pdet and QoL.

Disclosures
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