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DECREASE OF URINARY NERVE GROWTH FACTOR BUT NOT BRAIN-DERIVED NEUROTRPOPHIC FACTOR IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SUCCESSFULLY TREATED WITH INTRAVESICAL HYALURONIC ACID

Hypothesis / aims of study

Interstitial cystitis/ bladder pain syndrome (IC/BPS) is a chronic inflammatory disorder of urinary bladder. A few studies of intravesical hyaluronic acid (HA) treatment for IC/BPS patients showed symptom improvement in a broad range between 30% and 85%. However, it lacked strong evidence to prove the anti-inflammatory effects of HA treatment for IC/BPS. Urinary neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) increased in IC/BPS patients, and could potentially be used as urinary biomarkers in the diagnosis and treatment prognosis of lower urinary tract diseases. This study was designed to investigate the changes of urinary NGF and BDNF levels in IC/PBS patients after HA treatment, and try to find out the potentially reliable biomarkers of IC/BPS.

Study design, materials and methods

From January 2009 to December 2010, thirty-three consecutive patients with IC/BPS were prospectively enrolled in this study, and a group of 45 age-matched normal subjects served as controls. All IC/BPS patients received 9 times of intravesical HA instillations in a 6-month treatment course, including 4 weekly intravesical instillations of 40 mg of HA (50 mL, 0.08%) followed by 5 monthly HA instillations. Urine samples were collected for measuring urinary NGF and BDNF levels at baseline and 2 weeks after the last HA treatment. Patients were also assessed for the VAS of pain, daily frequency and nocturia episodes, functional bladder capacity (FBC) and global response assessment (GRA). Patients with a GRA decrease of 2 after HA treatment was considered as responders. The urinary NGF and BDNF levels were compared between IC/BPS patients and the controls, and between the responders and nonresponders to HA treatment.

Results

The total NGF, BDNF, and NGF/Cr, BDNF/Cr levels were significantly higher in IC/BPS patients compared to the controls (Table 1). NGF and BDNF levels also showed significantly decrease after HA therapy (Table 1) Urinary NGF/Cr levels were significantly decreased in the responders with VAS reduction by >2 (34.1 ± 14.5 v 9.41 ± 5.21, p=0.03) and GRA improved by 2 (45.2 ± 25.7 v 4.53 ± 2.15, p=0.046), but not in non-responders. We did not find significant decrease of urinary BDNF in responders or non-responders after HA therapy.

Interpretation of results

Increased urinary NGF and BDNF levels in patients with IC/BPS suggest that chronic inflammation is involved in the pathogenesis of this bladder disorder. After HA treatment, the clinical symptoms (including VAS, FBC and GRA) improved and urinary NGF levels decreased significantly, indicating that HA could provide therapeutic effects to IC/BPS with decreased inflammation. HA could protect the bladder mucosa from bacterial adhesion and permeation of toxic substance. It could render an environment for the recovery from bladder inflammation, to avoid the vicious cycle of defective urothelium and suburothelial inflammation. Urinary NGF, but not BDNF, probably could potentially be a biomarker of IC/BPS in the diagnosis and monitoring the therapeutic effects, suggesting the different roles of neurotrophins in IC/BPS.

Concluding message

Urinary NGF and BDNF levels were significantly higher in IC/BPS patients compared to the controls. Urinary NGF, but not BDNF, levels decreased significantly after intravesical HA therapy. The reduction of urinary NGF levels was significant in responders with VAS reduction and GRA improvement. These results suggest the inflammation in IC/BPS bladders can be improved after HA therapy.

Table 1. Demographic data, Urinary NGF, NGF/Cr, BNDF, and BDNF/Cr levels between IC/BPS patients and control.

	Control (n=45)	**IC/BPS baseline (n=33)**	**IC/BPS after HA treatment (n=33)**	*P value	**P value
Gender	F:40, M:5	F:28, M:5			
Age	45.9 ± 2.08 (19~58)	46.9 ± 2.44 (16~61)		0.771	
Urinary NGF (pg/ml)	2.25 ± 0.91	92.39 ± 24.87	34.19±10.58	<0.001	0.04
UrinaryNGF/Cr(pg/ml)	0.37 ± 0.13	31.07 ± 11.98	8.13±2.81	<0.001	0.02
UrinaryBDNF (pg/ml)	9.57 ± 5.37	107.53 ± 40.81	64.09±21.01	<0.001	0.68
UrinaryBDNF/Cr (pg/ml)	4.82 ± 2.45	23.78 ± 7.70	17.22±7.37	<0.001	0.55
VAS		3.12 ± 0.43	1.79 ± 0.36		0.001
GRA		1.09 ± 0.15	1.85 ± 0.16		<0.001
FBC		170.6 ± 16.1	228.5 ± 20.5		0.004

* p value: comparison between control and IC/BPS baseline
** p value: comparison between IC/BPS at baseline and after HA treatment
VAS: visual analog score, GRA: global response assessment, FBC: functional bladder capacity; data are expressed as mean ± standard error

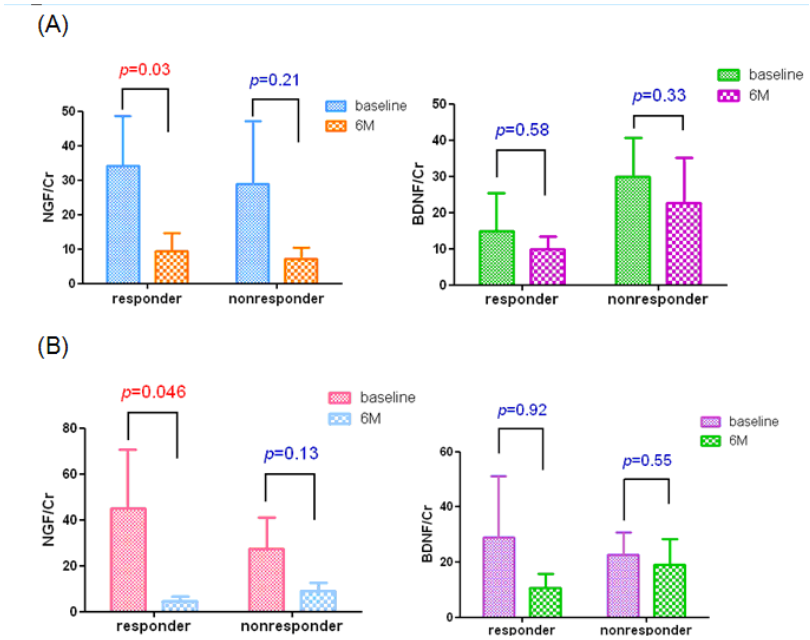

Fig. 1. The changes of urinary NGF/Cr and BDNF/Cr levels in the responders and non-responders defined by (A) VAS reduction by ≥2 and (B) GRA improvement by ≥2.

Disclosures
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