

ELEVATED URINARY LEVELS OF HEPATOCARCINOMA-INTESTINE-PANCREAS/PANCREATITIS-ASSOCIATED PROTEIN (HIP/PAP) IN PATIENTS WITH PAINFUL BLADDER SYNDROMES/INTERSTITIAL CYSTITIS (PBS/IC)

Hypothesis / aims of study

Painful bladder syndromes/interstitial cystitis (PBS/IC) is a chronic bladder inflammatory disorder. The etiology and pathophysiology of PBS/IC are not well understood. Some growth factors, cytokines and other factors that affect the proliferation of epithelial cells are assumed to elicit the pathogenesis of PBS/IC (1, 2).

Previously, we have demonstrated in a rat cystitis model that Pancreatitis-associated protein (PAP III) was expressed in the bladder urothelium (3). PAP III corresponds to Hepatocarcinoma-intestine-pancreas/ Pancreatitis-associated protein (HIP/PAP) in humans. Along with the progression of bladder inflammation, PAP III expression was increased (3). PAP III might play an important role as an anti-inflammatory factor in cystitis. From this background, we hypothesize that human HIP/PAP is expressed in the bladder of patients with PBS/IC and released into the urine in PBS/IC patients. In this study, we measured urinary HIP/PAP levels of PBS/IC patients and analyzed associations between urinary HIP/PAP levels and the severity of urinary symptoms.

Study design, materials and methods

Patients with IC were diagnosed based on the National Institute of Diabetes and Digestive and Kidney Diseases clinical criteria.

The 24h urinary frequency and mean voided urine volume were assessed by a voiding diary and bladder pain on a verbal 11-point numeric rating scale (NRS). The NRS is a common pain scale for rating a patient's perceived pain intensity on a numeric scale from 0 to 10 with 0 representing no pain and 10 representing the worst pain.

Urinary specimens were collected from 27 female patients with PBS/IC and 27 female controls who were age matched to IC patients. Urinary HIP/PAP concentrations were measured by enzyme-linked immunosorbent assay (ELISA) (Dynabio, Marseille, France).

The association between urinary HIP/PAP levels and 24h urinary frequency, mean voided urine volume, and bladder pain was analyzed by Spearman's correlation coefficient by rank.

Results

Median Urinary HIP/PAP concentration in PBS/IC patients (median: 13.67 pg/ml) was significantly higher than in controls (median: 1.86 pg/ml) (Mann-Whitney's *U* test, $P < 0.0001$). In PBS/IC patients, urinary symptoms were examined and evaluated for their association with the urinary level of HIP/PAP. Urinary HIP/PAP levels in PBS/IC patients were significantly associated with 24h urinary frequency ($r = 0.429$, $p = 0.029$). An inverse association between urinary HIP/PAP levels and the mean voided urine volume in PBS/IC patients was also observed ($r = -0.488$, $p = 0.013$). The significant association between urinary HIP/PAP levels and bladder pain in PBS/IC patients was found on a VRS ($r = 0.443$, $p = 0.024$).

Interpretation of results

We have demonstrated that the urinary HIP/PAP levels in PBS/IC patients were apparently higher than those in normal controls. It is suggested that expression of HIP/PAP is induced in the urothelium and HIP/PAP is released into the urine in PBS/IC patients. Intriguingly, the urinary levels of HIP/PAP are correlated with the severity of urinary symptoms, implying that the level of HIP/PAP in urine might be involved in the pathogenesis of PBS/IC.

Concluding message

It is suggested that HIP/PAP is one of candidate biomarkers of PBS/IC and HIP/PAP is involved in the pathogenesis of PBS/IC.

References

1. Proc Natl Acad Sci U S A (2004) 101; 11803-11808
2. J Urol (2002) 167; 2461-2469
3. J Urol (2008) 179; 1603-1609

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Was this study approved by an ethics committee?	Yes
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Was informed consent obtained from the patients?	Yes