

A Feasibility Study to Determine Whether Clinical Contrast Enhanced Magnetic Resonance Imaging can Detect Increased Bladder Permeability in Patients with Interstitial Cystitis

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Purpose: Interstitial cystitis/bladder pain syndrome is a bladder pain disorder associated with voiding symptomatology and other systemic chronic pain disorders. Currently diagnosing interstitial cystitis/bladder pain syndrome is complicated as patients present with a wide range of symptoms, physical examination findings and clinical test responses. One hypothesis is that interstitial cystitis symptoms arise from increased bladder permeability to urine solutes. This study establishes the feasibility of using contrast enhanced magnetic resonance imaging to quantify bladder permeability in patients with interstitial cystitis.

Materials and Methods: Permeability alterations in bladder urothelium were assessed by intravesical administration of the magnetic resonance imaging contrast agent Gd-DTPA (Gd-diethylenetriaminepentaacetic acid) in a small cohort of patients. Magnetic resonance imaging signal intensity in patient and control bladders was compared regionally and for entire bladders.

Results: Quantitative assessment of magnetic resonance imaging signal intensity indicated a significant increase in signal intensity in anterior bladder regions compared to posterior regions in patients with interstitial cystitis ($p < 0.01$) and significant increases in signal intensity in anterior bladder regions ($p < 0.001$). Kurtosis (shape of probability distribution) and skewness (measure of probability distribution asymmetry) were associated with contrast enhancement in total bladders in patients with interstitial cystitis vs controls ($p < 0.05$). Regarding symptomatology interstitial cystitis cases differed significantly from controls on the SF-36®, PUF (Pelvic Pain and Urgency/Frequency) and ICPI (Interstitial Cystitis Problem Index) questionnaires with no overlap in the score range in each group. ICSI (Interstitial Cystitis Symptom Index) differed significantly but with a slight overlap in the range of scores.

Abbreviations and Acronyms

3D = 3-dimensional

BAI = Beck Anxiety Index

BDI-II = Beck Depression Inventory®-II

BMI = body mass index

BPS = bladder pain syndrome

CE-MRI = contrast enhanced MRI

IC = interstitial cystitis

MRI = magnetic resonance imaging

ROI = region of interest

SI = signal intensity

TSC-40 = Trauma Symptom Checklist-40

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Conclusions: Data suggest that contrast enhanced magnetic resonance imaging provides an objective, quantifiable measurement of bladder permeability that could be used to stratify bladder pain patients and monitor therapy.

Key Words: urinary bladder; cystitis, interstitial; permeability; magnetic resonance imaging; questionnaires

INTERSTITIAL cystitis/BPS is a bladder pain disorder associated with voiding symptomatology and other systemic chronic pain disorders.¹ Originally IC was considered rare and diagnosed on the basis of finding a Hunner lesion² but now the definition has broadened to include bladder pain, urgency and frequency syndromes.^{1,3} Cystoscopy biopsy and hydrodistension to observe petechial bleeding are no longer routinely performed,³ resulting in reduced use of imaging or physiological methods as objective, quantifiable criteria for diagnosis. IC/BPS prevalence has a 10:1 female-to-male ratio.¹ The condition is thought to be a type of hypersensitivity disorder that affects bladder and other somatic/visceral organs with many overlapping symptoms and pathophysiology or a continuum of painful vs nonpainful overactive bladder syndrome.¹ Two distinct pain location phenotypes for IC/BPS occur, including pelvic pain only in 19% of cases and pelvic pain beyond in 81% using pain diagnosis criteria.⁴ Also in 25% of individuals with IC an emotional component is associated with the physical concerns.⁵

Basic assessments for IC/BPS include medical history and physical examination, symptom questionnaires, evaluations of pain, urination frequency/volume and post-void residual urine, urinalysis, urine culture and cytology.¹ Characteristic clinical features of BPS include bladder filling pain and wall tenderness.⁶ For patients with symptoms associated with complicated IC/BPS further assessment for incontinence, gastrointestinal and/or gynecological signs/symptoms, microscopic/gross evaluation and other tests (eg imaging, cystoscopy and laparoscopy) need to be performed.¹ IC/BPS is essentially a diagnosis of several exclusion criteria.¹ Because they are associated with IC diagnosis, psychiatric illnesses such as depression, anxiety, addiction and a history of child abuse as well as bowel/gastrointestinal problems are also assessed.^{7,8}

Currently IC/BPS diagnosis is complicated as patients present with a range of symptoms, physical examination findings and clinical test responses.¹ A simple and conclusive diagnostic test to establish whether some structural abnormalities are associated with IC/BPS, such as bladder urothelial permeability, would provide a means to stratify or phenotype patients with lower abdominal pain and urinary voiding symptoms. Although to our

knowledge the etiology of the disorder is not known, a constant observation is that patients with IC have increased permeability, which enables urinary toxins to penetrate into the urothelium and muscularis. Earlier Parsons et al reported increased uptake of urea from the bladder of patients with IC vs controls.⁹ Buffington and Woodworth noted abnormal kinetics of excretion of fluorescein due to recycling from the bladder.¹⁰ Parsons et al also proposed a potassium sensitivity test in which a pain reaction due to instillation of dilute KCl (but not NaCl) was diagnostic of increased bladder permeability.¹¹

In this study we determined the feasibility of using CE-MRI to assess bladder permeability in a small cohort of patients with IC. A MRI contrast agent was introduced via an intravesical catheter to assess permeability alterations in bladder urothelium compared to that in normal controls. We suggest that CE-MRI could provide an objective assessment of bladder permeability alterations, which could be used to stratify patients with bladder pain and monitor therapy.

MATERIALS AND METHODS

Participants

Six IC cases and 4 controls participated in the study. IC cases were recruited by their physicians from the Female Pelvic Medicine and Bladder Health Clinic at University of Oklahoma Medical Center, Oklahoma City, Oklahoma, from 2013 to 2015. None of the patients with IC had recently been hydrodistended nor had they received any intravesical therapy. Healthy controls were recruited on campus via flyers. MRI measurements were not available for 1 IC case due to technical difficulties, leaving 5 IC cases. Signed informed consent was obtained from each participant in accordance with the University of Oklahoma Health Sciences Center institutional review board, which approved the study (Protocol No. 1684).

Clinical CE-MRI

All scans were performed on a 3.0 Tesla 70 cm wide bore GE® Discovery 450 clinical MRI system with a 50 mT/m and 200 Tesla/m/second gradient system. Pre-contrast and post-contrast Gd-DTPA (Magnevist®, 0.05 mmol/kg body weight, 5 ml in 200 ml total volume, diluted in sterile saline and instilled via an intravesical 16Fr silicone Foley catheter at 2 to 2.5 cc per second during 5 to 10 minutes) 2-dimensional T1-weighted spin echo images were obtained

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