



Role of Diffusion-Weighted Magnetic Resonance Imaging in the Diagnosis of Bladder Pain Syndrome/Interstitial Cystitis

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OBJECTIVE	To evaluate whether DW-MRI can contribute to noninvasive diagnosis of BPS/IC. The agreement between two raters (2 radiologists involved in the study) was also evaluated, the relevance of the "operator-dependent" factor defined.
PATIENTS AND METHODS	Twenty-two female patients with a diagnosis of BPS-IC were recruited and performed DW-MRI. The same investigation was also performed in 20 patients with pelvic gynecological diseases and no BPS-IC.
RESULTS	A significant difference was found between BPS-IC and no-BPS-IC since 17 out of 22 subjects of the first group were positive, compared to 3 out of 20 no-IC subjects, with a <i>P</i> value of .001 to highlight the statistical significance. The sensitivity of the exam was 77%, while the specificity was 85%. There was good agreement between the 2 raters in the evaluation of MRI results.
CONCLUSION	DW-MRI helps to obtain a noninvasive diagnosis of BPS/IC, by providing useful information on the choice of which patients may be more appropriately submitted to cystoscopy and bladder biopsy. UROLOGY 141: 55–59, 2020. © 2020 Elsevier Inc.

Bladder Pain Syndrome/Interstitial Cystitis (BPS-IC) is a clinical condition characterized by the sensation of pain, a sense of pressure and discomfort perceived as correlated with the bladder associated with at least 1 urinary symptom, usually urinary frequency and urgency lasting more than 6 months, with repeatedly negative urine culture.¹

The first epidemiological study was performed by Oravisto in Finland analyzing patients diagnosed in a population of 1 million people recruited into the study.² Prevalence was 18/100,000 in female population, 10.6/100,000 including both female and male patients, since 10% of the entire patient population were male. The diagnosis is made by combining clinical features with cystoscopy and

hydrodistension, which results in a severity progressing from 1 to 3, and with histologic examination of bladder biopsy, which allows to obtain a descriptive index of the disease.¹

In the context of chronic pelvic pain it is possible to define chronic pelvic pain syndrome, which may be associated with urologic, gynecologic, physiatric, neurologic symptoms. In the urologic field, pain can be perceived as associated with the testicle, epididymis, prostate, vagina, vulva, bladder and, in the latter case, the interstitial cystitis described according to the criteria stated by the European Association for the Study of Interstitial Cystitis (ESSIC), shared by the scientific community, can be included.

Some studies have evaluated the introduction of noninvasive imaging techniques in the diagnostic procedures, specifically MRI. In 2016, Towner et al³ analyzed the use of MRI with intravesical contrast to assess increased bladder permeability, observe the correlation with symptoms, and stratify and monitor patients' disease progress. Charlanes et al⁴ sought to determine whether patients with BPS/IC revealed bladder hyperintense signals with diffusion weighted-magnetic resonance imaging (DW-MRI).

PATIENTS AND METHODS

Twenty-two female patients with a diagnosis of BPS-IC, made by means of clinical features indicating BPS-IC underwent

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cystoscopy, hydrodistension, and bladder biopsy. Between January 2018 and March 2019, they were recruited and performed DW-MRI. The same investigation was also conducted in a group of 20 patients with benign pelvic gynecologic diseases and no BPS-IC, who were selected as controls to compare the radiological findings observed in the bladder wall study.

The exclusion criteria were:

- age <18 years
- confounding diseases (eg, pudendal neuropathy, etc.) according to ESSIC criteria⁵
- Recurrent urinary tract infections
- Pregnancy and breastfeeding
- Claustrophobia

The following parameters were evaluated: date of cystoscopy under sedation with hydrodistension and bladder biopsy including detrusor muscle, disease duration evaluated by means of the interval elapsed between the diagnostic procedure and the date of MRI, the degree of signal intensity, the sites where MRI signal intensity was detected in the bladder, the results of the SF-36 questionnaire including the following domains: physical activity, physical pain, general health, vitality, social activities, limitation of emotional role, mental health.

Validation studies showed that SF-36 has discriminating abilities between the normal population and patients with psychiatric diseases or physical disorders and allows to discriminate between groups of populations with severe medical conditions and groups with moderate disease. The index called Physical Component Summary (PCS) concerns the physical state, while the Mental Component Summary (MCS) index measures the mental state.

Pelvic DW-MRI of BPS-IC patients and controls were prospectively examined by 2 radiologists who were unaware of the medical diagnosis and MRI indication. For each case, the radiologist examined T2-weighted multiplanar images, DWI trace acquired with b-value of 800, 1000 or 1,200 s/mm². The signal intensity of the bladder wall in DW-MRI sequences was classified into: high signal intensity of the bladder wall, moderate signal, or no signal.

The primary objective of this prospective study is to evaluate whether DW-MRI can contribute to a noninvasive diagnosis of interstitial cystitis/bladder pain syndrome (BPS/IC).

Secondary objectives are

- a) to evaluate if there is a link between the duration of the disease and the DW-MRI signal.
- b) Evaluate the agreement between the raters (the 2 radiologists involved in the study) to define the relevance of the "operator-dependent" factor.
- c) Observe if there is an association between deterioration in quality of life (assessed with the Short Form 36 [SF-36]) questionnaire and signal intensity (which may be absent, moderate, or high).

Statistical Analysis

The associations between the qualitative variables were evaluated with the Fisher test; the chi-square test was used as a test for the linear trend of the proportions for the evaluation of the MRI signal intensity in the 2 different groups of patients.

The difference in the risk of disease assessment (with the respective 95% confidence interval) between the group of patients reporting a magnetic resonance signal and the group with no signal was also calculated.

Continuous variables were compared between the 2 groups with the nonparametric Mann-Whitney test, while comparisons between 2 groups (high, moderate signal, and no signal) were performed with the Kruskal-Wallis test.

The concordance between the evaluations carried out with MRI and with cystoscopy was evaluated, and also correspondence between signal evaluations of 2 different raters was calculated with the Cohen kappa coefficient, with 95% confidence interval.

All tests are 2-sided. The significance level was set at alpha = 0.05. Statistical analyses were performed with the STATA software version 15.0 (StataCorp, College Station, TX).

RESULTS

In Table 1, we find the global descriptive statistics of age and disease duration for the whole sample and for each group: patients with IC vs no-IC. The median age is 49.97 years with an interquartile range (between first and third quartiles, or between 25th percentile and 75th percentile) which corresponds to p₂₅ = 35.50 and p₇₅ = 64.50. The median age of the group with IC corresponds to 45.73 years, while that of no-IC women was 53.71 years, with P value .1989, it can be observed that there is no significant age difference between the 2 groups. Three patients with BPS/IC were excluded because lost to follow-up, in 1 case a mass of uncertain origin was accidentally found (which represented an exclusion criterion), 2 patients could not be evaluated due to incomplete bladder filling, inadequate for MRI evaluation.

Table 2 describes the presence of signal in the anterior bladder wall at DW-MRI (Fig. 1), the signal could be detected in 15 patients out of 22, which corresponds to 68.18% of patients with BPS-IC, compared to 3 out of 20 patients, that is 15% positivity in the control group. The P value = .005 confirms the statistical significance of this difference.

The right wall of the bladder has shown a prevalence of positive signal, although slightly less marked than that observed on the anterior wall (Supplementary Table 1). On the other hand, the difference between no-IC patients with no signal, 18 out of 20, compared to 2 no-IC patient with signal present, is significantly more evident. This suggests a high specificity of the exam, since with absent signal (Fig. 2) there is a high possibility that a

Table 1. Age and disease duration of IC and no-IC patients

	Total N. 42	No IC n = 20	IC n = 22	P Value
Age	49.97 y (35.50-64.50)	53.71 y (43-68)	45.73 y (32-61)	.1989
Disease duration	30.31 (9-23) months		30.31 (9-23) months	

Table 2. Comparison between patients with IC and no-IC patients based on the location of the signal detected on DW-MRI in anterior bladder wall

Signal DW-MRI Anterior Bladder Wall	no IC	IC	Total
Signal absent	17 85%	7 31.82%	24
Signal present	3 15%	15 68.18%	18
Total	20	22	42

P value = .005.

bladder wall involvement of the disease is not identifiable, the incidence being calculated at 90%.

The data of the left lateral wall of the bladder are different from those obtained on the right wall, the percentage of DW-MRI positive signal in the no-IC group was similar to that of IC group. The results of the signal in the posterior wall reflect the trend recorded in the previous analyses, but signal positivity was statistically not significant in IC group (*P* value = .263). Looking at the average duration of the disease, that is the time between

symptom onset and the date of cystoscopy with hydrodistension and biopsy, in relation to the intensity of the signal, it can be seen that disease duration has no particular influence on the intensity of the signal. In fact, patients with a mean duration of 43.3 months had no signal, compared to those with a shorter duration of 20.7 months in patients with moderate signal and 32.6 months in patients with intense signal, the differences were not statistically significant (*P* = .82); however, the results could have been different in a larger number of patients.

[Supplementary Table 2](#) reports the data showing the impact of the disease on physical and mental health respectively. The categories of physical activity, limitations to the physical role, and physical pain for the first domain are reported in [Supplementary Table 3](#). [Supplementary Table 4](#) reports data on social activities, limitations of emotional role, mental health.

Primary endpoint- There is a clear difference of DW-MRI between IC group and no-IC group since 17 out of 22 IC cases were positive, compared to 3 out of 20 no-IC cases, with a *P* value of .001 to highlight the statistical significance. The sensitivity of the exam varies between 59% and 68% according to the site of its signal, while the specificity is between 85% and 90%.

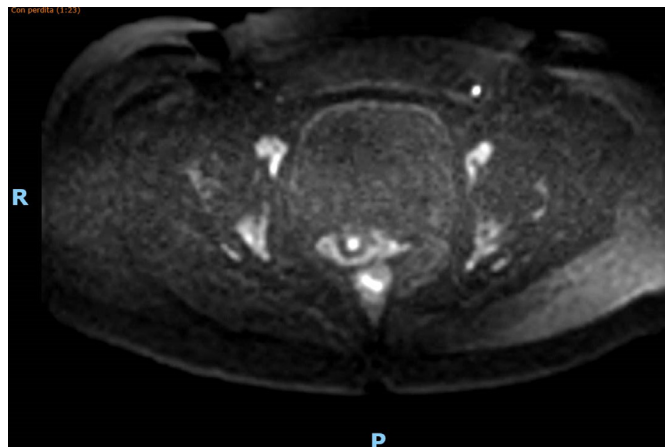


Figure 1. DW-MRI. Signal present in the anterior bladder wall in IC patient. (Color version available online.)

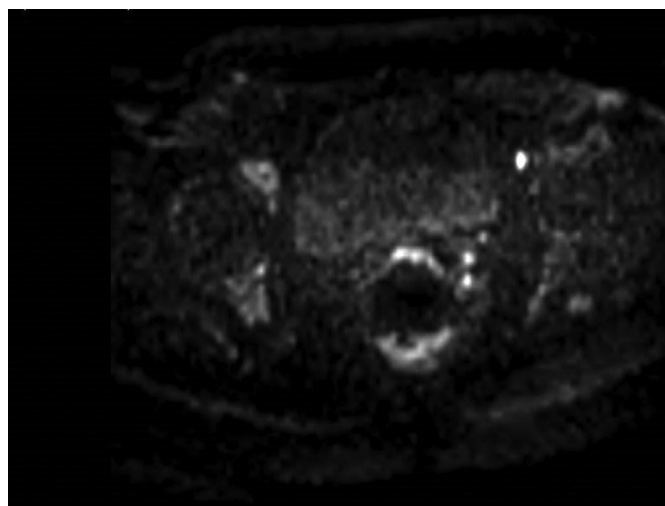


Figure 2. DW-MRI signal absent in the anterior bladder wall in no-IC patient.

The risk difference (RD) is calculated on these results, meaning that if a subject has a positive signal at DW-MRI he is likely to have a diagnosis of BPS/IC, there seems to be a risk difference between exposed (exposed risk = 0.81) and not exposed (unexposed risk = 0.17) being equivalent to RD = 0.64, with *P* value = .0008.

Supplementary Table 3 reports the results of the scores obtained from responses of patients to questionnaires, with an interquartile range, for 3 degrees of magnetic resonance signal: absent, moderate, and high. The scores are rather low both for the Physical Component Summary and for the Mental Component Summary compared to the average values in relation to sex and age, indicating the impact of the disease on the quality of life.

Secondary endpoints- Supplementary Table 5 shows the correlation of average duration of the disease (months) with the intensity of signal, and it shows no significant association between these 2 data.

The 2 radiologists are defined as "raters," blind to the diagnosis, who evaluated the MRI. There is good agreement between them in the evaluation of anterior and posterior walls (Supplementary Table 6), $K = 0.695$ e $K = 0.640$, and fair agreement in right and left lateral walls, with $K = 0.263$ e $K = 0.397$. No significant correlation resulted between DW-MRI signal and disease-related negative impact on Physical (Supplementary Table 7) and Mental Health Index of quality of life (Supplementary Table 8), measured with SF-36.

DISCUSSION

Unlike a recent study by another author⁴ on DW-MRI, the first in IC/BPS patients, we carried out our study using the reports of 2 different radiologists who were unaware of the diagnosis, therefore blind, the correlation between the 2 radiologists was evaluated together with the degree of operator-dependency of the exam.

Patients on average had been diagnosed 30 months after symptom onset, and they had started treatment once the diagnosis was made. The global analysis of the absence or presence of a signal on the bladder walls shows a high specificity, it also highlights a high positive predictive value, since it is likely that if a patient has a positive magnetic resonance signal she actually has interstitial cystitis. These data are similar to the results reported by the Charlanes group.⁴

The interpretation of the RD leads to the conclusion that among subjects who present a positive DW-MRI signal the incidence of cases of interstitial cystitis is higher, and there is a statistically significant difference compared to patients who do not have a high DW-MRI signal. Having a positive signal is therefore suggestive of interstitial cystitis.

Patients were analyzed based on the type of signal detected: absent, moderate, and high. It should be noted that in the anterior bladder wall, when gathering patients with moderate and high signal in a single group, that is signal present, 17 patients have no signal in 20 no-IC patients, while 15 out of 22 IC patients have signal present (Table 2).

A statistically significant trend (*P* value = .001) is noticeable, which shows that the more intense the signal,

the more likely is that it is related to an inflamed bladder wall, and vice versa. In fact, in IC group there are 5 patients with absent signal, 4 with moderate signal and 11 with high signal intensity, compared to 17 patients with absent signal, 2 with moderate signal and 1 with high signal intensity of the no-IC group. In follow-up studies of the pelvis, it has been suggested that when performing DW-MRI study the bladder filling should be standardized and antiperistaltic drugs should be administered to avoid misinterpretation and bowel motion artifacts. In the female pelvis⁶ in fact it is likely that the distension of the bladder wall due to filling can alter the quality and intensity of the signal. DW-MRI is a noninvasive investigation, its features have recently been expanded to applications related to pelvic imaging, including diagnostic investigation of pelvic tumours.⁷⁻⁹ DW-MRI could also provide information in the evaluation of treatment response comparing to other sequences in muscle-invasive bladder cancer.¹⁰ Similarly, it could provide useful information in treatment response of BPS/IC in terms of signal intensity.

Our study had a prospective design, the pain score was available when DW-MRI was performed. However, as in the study by Charlanes,⁴ the bladder volume during the MRI was not standardized, and this may represent a limitation.

Two different radiologists, blind to the diagnosis, independent of each other carried out the DW-MRI analysis, and they classified the report in 3 subjective categories (no signal, moderate, and high signal).

The analysis of the bladder wall signal with DW-MRI, reflecting the inflammatory bladder wall tissue, could help to divide BPS/IC into subclasses. Besides, the definition of an apparent diffusion coefficient (ADC) cutoff, and an analysis of its variation with treatment would represent a further future step of the study.

CONCLUSION

The approach assessing the bladder using DW-MRI in IC/BPS patients may provide an additional diagnostic evaluation that could be used to stratify the wide spectrum of chronic pelvic pain, help to select patients to be assessed performing more invasive assessments, such as cystoscopy with hydrodistension and bladder biopsy, it could also prove particularly useful in clinical trials and for monitoring the efficacy of therapy.

The study has been approved by the appropriate institutional and/or national research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2020.03.019>.

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