Women Undergoing Third Line Overactive Bladder Treatment Demonstrate Elevated Thermal Temporal Summation

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Purpose: We sought to determine whether women with overactive bladder who required third line therapy would demonstrate greater central sensitization, indexed by temporal summation to heat pain stimuli, than those with overactive bladder.

Materials and Methods: We recruited 39 women with overactive bladder from the urology clinic who were planning to undergo interventional therapy for medication refractory overactive bladder with onabotulinumtoxinA bladder injection or sacral neuromodulation. We also recruited 55 women with overactive bladder who were newly seen at our urology clinic or who responded to advertisements for study participation. Participants underwent quantitative sensory testing using a thermal temporal summation protocol. The primary study outcome was the degree of temporal summation as reflected in the magnitude of positive slope of the line fit to the series of 10 stimuli at a 49C target temperature. We compared the degree of temporal summation between the study groups using linear regression.

Results: Women in the group undergoing third line therapy showed significantly higher standardized temporal summation slopes than those in the nontreatment group ($\beta = 1.57$, 95% CI 0.18–2.96, $t = 2.25$, $p = 0.027$). On exploratory analyses a history of incontinence surgery or hysterectomy was associated with significantly greater temporal summation.

Conclusions: In this study the degree of temporal summation was elevated in women undergoing third line overactive bladder therapy compared to women with overactive bladder who were not undergoing that therapy. These findings suggest there may be pathophysiological differences, specifically in afferent nerve function and processing, in some women with overactive bladder.

Key Words: urinary bladder, overactive; urinary incontinence, urge; central nervous system sensitization; postsynaptic potential summation; patient reported outcome measures

Abbreviations and Acronyms

CS = central sensitization

ICIQ-FLUTS = International Consultation on Incontinence Modular Questionnaire-Female Lower Urinary Tract Symptoms

OAB = overactive bladder

OAB-q = OAB Questionnaire

PROMIS = Patient-Reported Outcomes Measurement Information System

TS = temporal summation

VAS = visual analog scale

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OVERACTIVE bladder is a common condition affecting American women.[1] However, the etiology of OAB remains unclear and likely involves inherent elements of the bladder and functional aspects of motor and sensory nerve innervation.[2] In line with the afferent nerve hypothesis,[2] it is plausible that any condition which promotes increased responses to

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normal or abnormal stimuli may contribute to the development of or exacerbate existing OAB. We have postulated that CS, a phenomenon well described in the chronic pain literature in which afferent C-fiber circuits display hyperresponsiveness,[3] may have such a role in certain individuals with OAB.[1]

We previously reported that compared to women without OAB those with OAB who required third line therapy with onabotulinumtoxinA bladder injection or sacral neuromodulation showed greater thermal cutaneous TS, that is increasing perceived pain in response to rapid repetition of the same stimulus intensity.[4] Because elevated TS is believed to be a marker for CS,[5,6] this finding suggested elevated CS in patients with OAB when compared to nonOAB controls.

Our current hypothesis was that CS may contribute to why some women with OAB are more likely than others to be refractory to first and second line OAB therapy. As the next step in this line of investigation, the aim of the current study was to determine whether women with OAB undergoing third line therapy would show greater TS than women with OAB not undergoing these treatments.

MATERIALS AND METHODS

After obtaining institutional review board approval we recruited 39 women 18 years old or older with OAB from the urology clinic who were planning to undergo onabotulinumtoxinA bladder injection or sacral neuromodulation. We also recruited 55 women with OAB, which was confirmed by a score of 4 or greater on the OAB-V3 (OAB-Version 3) awareness tool,[7] who were newly seen at our urology clinic or who responded to community advertisements and were not undergoing third line therapy.

We excluded women from analysis if they were diagnosed with a neurological condition that might contribute to urinary symptoms (eg spinal cord injury, multiple sclerosis, stroke or autonomic dysfunction), had a history of bladder cancer, pelvic irradiation or bowel diversion, or were unable or unwilling to complete all study protocols. We also excluded women with interstitial cystitis/bladder pain syndrome based on medical record review and/or whether they met the RICE (Rand Interstitial Cystitis Epidemiology) case definition.[8]

Participants completed a standardized questionnaire assessing demographics and medical history, including age, race/ethnicity, highest education level, general health, prior history of incontinence surgery, hysterectomy or prolapse surgery and whether they were receiving OAB medications. We assessed pelvic surgical history with yes or no questions, that is, "Have you ever had…?" a hysterectomy, an operation to remove the uterus or womb, or surgery for incontinence (urine leakage) or to repair pelvic organ prolapse (pelvic floor disorder, cystocele or rectocele).

Participants also completed the OAB-q[9] and the ICIQ-FLUTS.[10] To assess psychosocial and somatic characteristics they completed the NIH (National Institutes of Health) PROMIS short form, version 1.0 instruments for depression (8a), anxiety (8a) and pain intensity(3a) as well as the SSS-8 (Somatic Symptom Scale-8).[11] We also assessed the presence of comorbid functional somatic conditions by self-report (ie low back pain) or by validated patient reported diagnostic measures, including migraine headache,[12] fibromyalgia[13] and irritable bowel syndrome.[14]

Quantitative Sensory Testing

All quantitative sensory testing protocols was done using a TSAII NeuroSensory Analyzer (Medoc, Minneapolis, Minnesota) with a 9 cm^2 Peltier thermode applied to the volar forearm. To determine heat pain threshold and tolerance levels we performed a series of 4 pain trials during which the probe temperature increased from a baseline temperature of 32C at a rate of 0.5C per second. In the heat pain threshold test the participant indicated the temperature at which the heat was first perceived as painful. In the heat pain tolerance trials the participant indicated when the pain became intolerable. We then separately derived the means of the 4 threshold and tolerance trials.

Our quantitative sensory techniques to measure TS are similar to those that are standard in the pain literature.[6,15] They were previously detailed in the context of OAB.[4] Briefly, we administered a sequence of 10 successive 0.5-second heat pulses to the forearm, during which the temperature rapidly increased and decreased from a temperature of 40C to 49C at a frequency of 0.4 Hz. This frequency is known to elicit C-fiber mediated temporal summation in the dorsal horn of the spinal cord. Immediately after the peak of every heat pulse the subjects provided a verbal numerical pain intensity rating using a VAS on a scale of 0—no pain or warmth to 100—worst possible pain. The standardized slope of the change in pain ratings over the series of 10 stimuli was derived for each patient as a TS index. A positive slope (greater than 0) indicated the presence of TS while a negative slope (less than 0) indicated habituation.

Statistical Analyses

Statistical analyses were performed with Stata/SE™ 14.1. We used the Student t-test to compare continuous variables and the chi-square test for categorical variables. Our independent variable in all primary analyses was the OAB group (OAB vs OAB undergoing third line therapy). We created linear regression models with the pain response index as the dependent variable (ie pain threshold, tolerance or TS), the OAB group as the independent variable, and patient age and the OQB-q score as control variables. To analyze TS we also included the initial VAS pain rating of the first TS stimulus to control for confounding due to baseline effects on observed slopes (ie ceiling effects). Finally, we explored possible factors that may have been be associated with the observed degree of TS using linear regression models in which the TS slope was the dependent variable. Analyses were done with 2-tailed $p < 0.05$ considered statistically significant.