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Temporal summation to thermal stimuli is elevated in women with Overactive Bladder Syndrome

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Abstract

Introduction—This study sought to provide a preliminary assessment of whether spinally-mediated afferent hyperactivity (i.e. central sensitization) might contribute to manifestations of Overactive Bladder Syndrome (OAB) in women as indexed by elevated temporal summation of evoked heat pain stimuli.

Methods—We recruited 20 adult women with OAB who were planning to undergo interventional therapy for OAB with either onabotulinumtoxinA injection or sacral neuromodulation and 23 healthy controls without OAB symptoms to undergo quantitative sensory testing with cutaneous thermal pain temporal summation. The primary study outcome was the degree of temporal summation, as reflected in the magnitude of positive slope of the line fitted to the series of 10 stimuli at the 49°C target temperatures. Linear regression and analysis of covariance were utilized to compare the degree of temporal summation between study groups.

Results—The standardized slope of temporal summation trials for women with OAB was significantly higher than for Controls (beta = 3.43, 95% confidence interval = 0.6 – 6.2, p = .017). The adjusted means $\pm$ SE of the standardized temporal summation slopes for the full OAB and Control groups were $3.0 \pm .5$ (95% confidence interval = 2.0, 4.1) and $1.7 \pm .5$ (95% confidence interval = .7, 2.7), respectively.

Conclusion—In this preliminary study, we demonstrated that women with OAB refractory to primary and secondary therapies exhibited greater thermal cutaneous temporal summation than women without OAB symptoms. This suggests that central sensitization, indexed by temporal summation, may be an underlying factor contributing to OAB in some women.

Mesh Terms/Key Words

overactive bladder syndrome; OAB; temporal summation; wind-up; central sensitization; quantitative sensory testing

Introduction

Idiopathic overactive bladder syndrome (OAB) represents a significant public health burden, as it affects one out of 6 U.S. adults, accounts for \$66 billion in total annual U.S. societal costs, and can be difficult to treat effectively (1). While the etiology of OAB remains unclear, a substantive body of animal and *ex vivo* research implicates increased afferent nerve activity (including activation of normally quiescent c-fibers) and altered CNS processing of excitatory signals contribute to OAB pathophysiology (2, 3). However, a reliable means to assess such changes in individuals with OAB has remained elusive, and thus whether and how these pathophysiologic mechanisms might contribute to clinical OAB manifestations, impart resistance to primary and secondary therapies, and influence treatment outcomes are unknown. Presently with no objective marker for OAB diagnosis, prognosis, or treatment response, there is a disconnect between scientific research findings on disease mechanisms and principles of patient management.

We hypothesize that one mechanism that may contribute to OAB in some women is central sensitization (4), which is an induced state of spinal hypersensitivity and a well-recognized mechanism of centrally-amplified pain perception (5). While pain is not generally associated with OAB and the absence of bladder pain typically distinguishes OAB from IC/BPS, up to 40% of women with OAB will describe their urgency as due to pain, pressure, or discomfort, as opposed to attributing it to fear of incontinence (6, 7). This suggests that some women with OAB may have an increased susceptibility to perceptions of pain, consistent with presence of central sensitization. Conceptually, central sensitization is not necessarily limited to pain, but involves hypersensitivity to low-threshold afferent signals including those that are not generally experienced as painful. In the case of OAB, central sensitization might alter processing of normal afferent signals conveying pain, mechanosensation, chemical sensitivity and motor/sensory functioning to the central nervous system during the micturition cycle (i.e. “afferent noise”) (8). This is consistent with the idea that OAB is a hypersensitivity syndrome related to dysfunctional afferent hyperactivity (7, 9, 10). Central sensitization is proposed to underlie the pathophysiology of several, usually painful, disorders often referred to as “central sensitivity syndromes,” such as fibromyalgia, irritable bowel syndrome, migraine, idiopathic low back pain, and interstitial cystitis/bladder pain syndrome (IC/BPS), among others (11, 12). These are considered a spectrum of overlapping conditions with a common pathophysiology of central nervous system hypersensitivity, increased afferent responsiveness, and visceral organ cross-talk (11).

The presence of central sensitization, as indexed by the phenomenon of temporal summation, is routinely measured using quantitative sensory testing (QST) (13–15). Temporal summation refers to an increase in pain perception in response to a repetitive series of brief noxious stimuli delivered at a constant intensity and frequency that elicits c-

fiber firing and activation of second-order spinal neurons (termed “wind-up”) (13). Temporal summation is presumed to be the psychophysical manifestation of central sensitization and is the most widely accepted index for measurement of central sensitization in the human pain literature (15). To our knowledge, temporal summation has never been studied in women with OAB, but it would be the measure of choice to investigate the presence of central sensitization in this population. The current study sought to provide a preliminary test of whether spinally-mediated afferent hyperactivity, central sensitization, might contribute to manifestations of OAB in women. Specifically, we used QST to evaluate whether women scheduled to undergo treatment with onabotulinumtoxinA or sacral neuromodulation for OAB demonstrate elevated temporal summation of evoked heat pain stimuli compared to healthy controls.

Materials and Methods

After obtaining Institutional Review Board approval, we recruited 20 adult women with OAB from the Urology clinic who were planning to undergo interventional therapy for medication refractory OAB with either onabotulinumtoxinA bladder injection or sacral neuromodulation. The OAB sample included women 18 or older with OAB as determined by their treating physician, but confirmed with a score of ≥ 4 on the OAB-V3 awareness tool, a validated 3-item screening tool with a sensitivity of 82% and specificity of 91% for OAB diagnosis (16). For comparison, we also recruited 23 women without a diagnosis of OAB (confirmed with a OAB-V3 score <4) from our Institutional community to serve as healthy controls. Women were excluded if they had diagnoses of neurologic conditions that might contribute to their urinary symptoms (e.g. spinal cord injury, multiple sclerosis, stroke, autonomic dysfunction), had a history of bladder cancer, pelvic irradiation, or bowel diversions, or were unable or unwilling to complete all study protocols.

Participants completed a standardized questionnaire assessing demographics and medical history, including: age, race/ethnicity, highest level of education, height and weight to calculate body mass index (BMI), and current OAB therapy. Participants also completed psychometrically-validated questionnaires documenting urinary symptoms and condition-specific health related quality of life, including the Overactive Bladder Questionnaire short-form (OABq-SF) (17), and the International Consultation on Incontinence Modular Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) (18). Additional standardized information on symptoms of urgency included a single item from the Interstitial Cystitis Epidemiology questionnaire: “Would you say this urge to urinate is mainly because of pain, pressure, or discomfort or because you are afraid you will not make it to the bathroom in time to avoid wetting?” (6) To assess psychosocial characteristics, participants completed the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) short form v1.0 instruments for depression (8a), anxiety (8a) and pain intensity (3a). Subjects also completed the Somatic Symptom Scale-8 to document general somatic symptom burden (19).

Our QST techniques to measure temporal summation are previously described (14, 20, 21). Briefly, we used a Medoc TSAII NeuroSensory Analyzer (Medoc U.S., Minneapolis, MN) with a 9-cm² peltier thermode that administers a standardized oscillating thermal stimulation

protocol designed specifically to elicit C-fiber mediated temporal summation. A sequence of 10 successive heat pulses (each 0.5 second in duration) was applied to the dominant ventral forearm with the thermode in a fixed position. During the sequence, the temperature rapidly increased from a baseline temperature of 40°C to the target temperature of 49°C with rapid return to baseline at a frequency of 0.4 Hz, a frequency known to elicit C-fiber mediated wind-up in the dorsal horn of the spinal cord. Immediately after the peak of every heat pulse within the sequence, subjects provided a verbal numeric pain intensity rating using a 0 – 100 visual analog scale (VAS) anchored with 0 = “No Pain or Warmth” and 100 = “Worst Possible Pain.” Before the actual test, participants underwent a practice session to acclimate them to the protocol and pain ratings. The standardized slope of change in pain ratings over the series of 10 stimuli was derived for each patient (using within-subject regressions in preliminary analyses) as an index of temporal summation to serve as a quantitative marker of the degree of central sensitization.

Statistical analyses were performed using Stata/SE 14.1 (StataCorp, College Station, TX). Primary analyses were conducted using linear regression and analysis of covariance, as previously published.(14, 20, 21) The primary study outcome (dependent variable) was the degree of temporal summation elicited, as reflected in the magnitude of positive slope of the line fitted to the series of 10 stimuli at the 49°C target temperatures. A positive slope (i.e. slope > 0) demonstrates the presence of temporal summation, while a negative slope (i.e. slope < 0) denotes temporal decrease in second pain (i.e., habituation). A subject was characterized as no change if the slope was equal to zero (15). The independent variable was Group (OAB vs. Control), dummy coded as 0 and 1. Based on results of preliminary analyses showing Group differences in baseline pain sensitivity, primary temporal summation analyses included initial VAS pain score at the first heat trial to control for confounding due to baseline effects on observed slopes (i.e., floor or ceiling effects). Secondary analyses examined the associations between a self-reported prior diagnosis of IC/BPS and primary outcomes. Analyses used a two-tailed $p < .05$ criterion for statistical significance.

Results

We enrolled 20 women with OAB and 23 women without OAB (Controls) between January 1, 2015 and March 1, 2016 to participate in the study. Demographic and clinical data are presented in Table 1. Women with OAB were older and had higher BMI than Controls. Women with OAB also reported higher PROMIS overall pain intensity and anxiety scores, and higher somatic symptom scores on the somatic symptom scale-8 than Controls. As would be expected, women with OAB reported greater OAB symptom burden and lower OAB-specific health related quality of life than controls, in addition to greater overall urinary symptoms and use of OAB medications (Table 2).

During the temporal summation protocol, women with OAB reported significantly higher VAS pain intensity ratings at the first heat trial compared to Controls (42.0 ± 28.4 versus 28.7 ± 15.7), with this difference nearly significant ($p = .06$). In the OAB group, two subjects had negative slopes (i.e. temporal decrease in pain), one had no change in pain ratings, and 17 (85%) had positive slopes (range .1 – 10.0). In the Control group, three subjects had no

change and 20 (87%) had positive slopes (range .3 – 5.0) ($p=.3$ for comparison between groups). Primary regression analyses controlling for the group differences in baseline pain response levels indicated that the standardized slope of temporal summation trials for women with OAB was significantly higher than that for Controls (beta = 3.43, 95% confidence interval = 0.6 – 6.2, $p = .017$). The adjusted means $\pm$ SE of the standardized temporal summation slopes for the full OAB and Control groups were $3.0 \pm .5$ (95% confidence interval = 2.0, 4.1) and $1.7 \pm .5$ (95% confidence interval = .7, 2.7), respectively (Figure 1). Among only those individuals exhibiting some degree of temporal summation (i.e., a positive slope), those in the OAB group exhibited significantly larger temporal summation slopes ($3.6 \pm .5$) than did the healthy controls ($1.9 \pm .5$; beta = 3.08, $p = 0.025$). Conducting primary regression analyses again using including main and interactive effects of age and BMI in the model did not alter the pattern of findings reported above (data not shown).

Exploratory analyses on the OAB subgroup revealed that seven of the women with OAB (35%) had a prior, self-reported diagnosis of IC/BPS. Details of this diagnosis were not available, such as the current status of their condition or whether the women were receiving ongoing treatment. As specified by the study criteria, all were undergoing third-line OAB therapy specifically for refractory OAB symptoms. OAB symptoms and health-related quality of life were slightly worse for IC/BPS compared to OAB, but not statistically different: mean OABqSS was 71 ± 25 vs. 65 ± 24 ($p=.6$) and mean OABqHRQL was 22 ± 21 vs. 33 ± 21 ($p=.3$), respectively. When analyzed separately from women with OAB, standardized temporal summation slopes were significantly higher for women with a history of IC/BPS compared to healthy controls ($4.0 \pm .9$ vs. $1.7 \pm .5$, $p = .02$), with nonsignificant elevations compared to women with OAB ($4.0 \pm .9$ vs. $2.5 \pm .7$, $p = .6$). (Figure 2) When women with prior IC/BPS were excluded from primary analyses, temporal summation slopes for women with OAB remained significantly higher than controls (beta = 3.18, 95% CI .4 – 6.0, $p=.027$).

Discussion

In this preliminary study of women with refractory OAB planning to undergo treatment with onabotulinumtoxinA or sacral neuromodulation, results confirmed our hypothesis that women with OAB would demonstrate elevated temporal summation of evoked heat pain stimuli compared to women without OAB. A subset analysis found that women with OAB who also reported a history of IC/BPS displayed significantly higher temporal summation compared to controls, and directionally but nonsignificantly higher levels compared to OAB group not reporting IC/BPS. Excluding the former subgroup from the primary analyses did not change the overall pattern of findings, suggesting that, at least in some women with OAB, central sensitization, as indexed by temporal summation, is present and may be a contributing factor underlying their condition.

The finding of elevated temporal summation provides clinical evidence of c-fiber hyper-responsiveness in OAB. This pattern is consistent with central sensitization, a phenomenon that develops when repetitive activation of afferent C-fibers results in conditioning of second-order neurons in the dorsal horn of the spinal cord, that in turn amplify afferent

signals from low-threshold A β and A δ mechanoreceptors and nociceptive C-fibers (i.e. heterosynaptic potentiation) (5). Once central sensitization develops, stimuli that generally do not provoke pain can produce pain (i.e. allodynia) and stimuli that normally provoke pain can produce pain at higher intensity (i.e. hyperalgesia). Sensitivity can also be increased even without pain (i.e. hyperesthesia). These changes known to occur in central sensitization appear to closely parallel the pathophysiologic changes observed in OAB, which can be broadly characterized as abnormally increased afferent signals from the bladder and decreased capacity to handle afferent signals in the central nervous system (2, 3).

From animal studies of detrusor overactivity that approximate OAB, “silent” bladder afferent C-fibers, which do not participate in normal physiologic bladder function and usually only respond to high-intensity activation (i.e. extreme distension, cold, heat or chemical irritation), become spontaneously active and hypersensitive to low intensity input (2, 3, 22). Once “sensitized”, even A δ mechanoreceptors demonstrate increased signaling at lower thresholds, although the exact nature of these changes remains unknown (3). As we have previously highlighted, this suggests possible relevance of central sensitization even to ostensibly non-painful conditions, such as OAB (4). At present, we can only speculate as to any source of persistent C-fiber input that might first initiate central sensitization in OAB, but investigators have suggested roles for urinary tract infection, urinary retention, and other precipitating events, which could represent the requisite high-threshold stimulation for the “silent” bladder C-fiber activation needed for central sensitization induction (23–25).

In the current study, we compared mean temporal summation levels between women with and without OAB. However, we do not interpret the findings of elevated temporal summation in the OAB group as implying that every woman with OAB necessarily has heightened central sensitization. Instead the findings suggest that there may be a subset of women with OAB who manifest central sensitization with elevated temporal summation as an underlying pathophysiologic mechanism. Furthermore, OAB in the context of a self-reported history of IC/BPS appears to be associated with somewhat greater temporal summation, suggesting that IC/BPS and OAB, while related in some ways, may be distinguished by underlying mechanisms. OAB is understood to encompass a range of potential underlying etiologies of various contributions; central sensitization may be just one factor for a subset of women. Given our study sample, which was a group of women with medication refractory OAB and moving to third line therapy, central sensitization may be contributing factor to resistance to medical and behavioral OAB therapy. Given our findings of associations with higher pain levels and somatic symptom burden in our sample of women with OAB, we propose that a potential subtype likely manifests with multiple somatic comorbidities and chronic pain conditions.

As noted above, temporal summation is the most widely accepted index for measurement of central sensitization (13, 15), and investigators from our team have successfully applied this technique to the study of other visceral conditions, including functional abdominal pain (14, 20, 21). However, to our knowledge, our study is the first to apply this psychophysical laboratory technique commonly used in chronic pain research to women with OAB. Therefore, there are few data with which to compare our results. Nevertheless, in studies using similar temporal summation protocols, including those published by our own research

team, findings of temporal summation in healthy controls are consistent with results for controls in our study, which lends reassurance to the reproducibility of our methods (14, 15, 20).

This study has limitations that must be considered when interpreting the findings. Our protocol utilizes cutaneous thermal stimulation during QST, but other modalities are available, such as mechanical or pressure stimulation. It is unknown whether a different modality would result in similar findings. Our study is cross-sectional in design and thus cannot address temporal associations between the onset of OAB symptoms and development of central sensitization. Prospective studies with repeated analyses are needed to investigate the cause and effect of elevated temporal summation and OAB. The results may not be generalizable to other groups of women with OAB, as our study sample was a highly symptomatic group of women undergoing third-line therapy for OAB drawn from a tertiary care Urology practice. Additional studies are needed using different samples of women with varying severity of OAB. Exploratory, secondary analyses in the current study identified some differences in women with a self-reported history of IC/BPS that are hypothesis generating. As a comparison of women with IC/BPS and OAB was not the primary intent of the study, we cannot examine this relationship further in the current dataset; dedicated studies comparing women with IC/BPS and OAB are needed to more appropriately study potential differences between these groups.

Despite these limitations our findings in the current study may be significant for the care of women with OAB. Not only do the results suggest that central sensitization may be present in some women with OAB, the findings raise the possibility that central sensitization contributes to OAB in women with the most difficult-to-manage or refractory symptoms. However, if confirmed, temporal summation could serve as an objective marker to help direct OAB therapy, for example, by identifying patients unlikely to benefit from pharmacologic interventions and most likely to benefit from interventional therapies, such as onabotulinumtoxinA or sacral neuromodulation. Additional studies specifically examining the predictive ability of temporal summation on treatment outcomes are warranted.

Conclusions

In this preliminary study, we demonstrated that women with OAB refractory to pharmaceutical management and electing to undergo either onabotulinumtoxinA bladder injection or sacral neuromodulation exhibited greater thermal cutaneous temporal summation than women without OAB. This suggests that central sensitization, as indexed by temporal summation, may be an underlying factor contributing to OAB in at least some women. This finding may have important future implications for understanding pathophysiology of OAB and for management of women affected by OAB, as this measure may be one of the first objective and noninvasive markers for mechanisms contributing to human OAB.

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Figure 1.

Adjusted mean slopes fitted to VAS pain ratings during temporal summation trials at 49° C for women with OAB and Controls. Women with OAB demonstrated a greater degree of temporal summation than Controls as represented by a higher slope (3.0 vs. 1.7, $p = .017$).

Figure 2.

Comparison of means of temporal summation slopes for controls, women with OAB, and a subset of women indicating a self-reported history of IC/BPS. Bar represents the adjusted mean slope and spike the 95% confidence interval. Significant differences ($p < .03$) from controls indicated by the asterisk.

Table 1

Demographic and clinical data for study cohort, N (%) except where noted.

	Control	OAB	(P)
	23	20	
Age, mean ($\pm$ SD)	42.1 (14.5)	56.1 (11.2)	.001
Race/Ethnicity			
NH White	22 (96)	16 (80)	.16
NH Black	0	3 (15)	
Other	1 (4)	1 (5)	
Highest education			
Less than high school	0	1 (5)	.32
High school graduate	2 (9)	5 (25)	
Some college or Associates degree	10 (44)	6 (30)	
College Graduate	7 (30)	7 (35)	
Graduate or professional degree	4 (17)	1 (5)	
Body Mass Index (kg/m ²)			
<25	16 (69)	0	<.001
25–29	2 (9)	4 (20)	
≥ 30	5 (22)	16 (80)	
PROMIS Pain intensity score, mean ($\pm$ SD)	40.4 (8.7)	48.9 (10.5)	.006
PROMIS Anxiety score, mean ($\pm$ SD)	48.2 (8.5)	56.1 (10.0)	.008
PROMIS Depression score, mean ($\pm$ SD)	46.1 (8.2)	51.5 (9.5)	.05
Somatic Symptom Score – 8, mean ($\pm$ SD)	5.7 (5.2)	15.1 (6.1)	<.001

Table 2

Lower urinary symptoms in study cohort.

	Control	OAB	(P)
OAB Medications	0	8 (40%)	.001
“Would you say this urge to urinate is mainly because of...?”			
Pain, pressure, or discomfort	9 (39)	3 (16)	<.001
You are afraid you will not make it to the bathroom in time to avoid wetting	0	5 (26)	
Neither	14 (61)	0	
Both	0	11 (58)	
OABq-SS, mean ($\pm$ SD)	4 (5)	67 (25)	<.001
OABq-HRQL, mean ($\pm$ SD)	99 (4)	29 (21)	<.001
ICIQ-FLUTS, mean ($\pm$ SD)	3 (3)	22 (8)	<.001