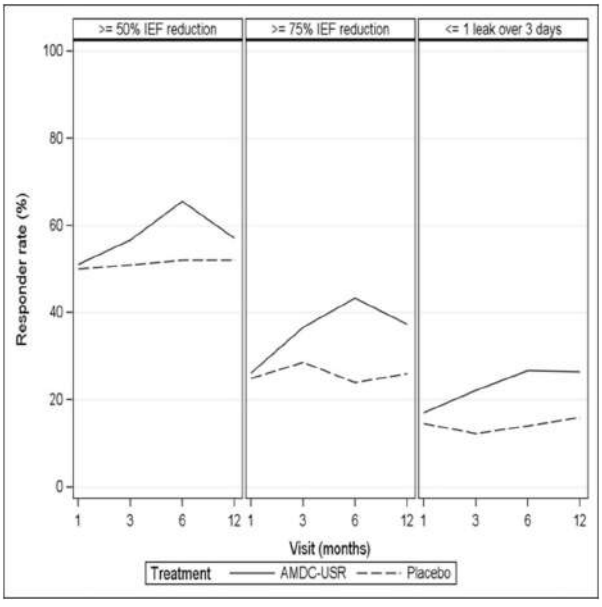
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intrasphincteric injection of 150 x 10^6 AMDC-USR or vehicle placebo and 1:1 to receive 1 or 2 treatments. Second treatments were administered 6 months after first treatments. At baseline and follow-up, SUI was monitored by 3-day diaries of stress incontinence episode frequency (IEF), 24-hour pad tests, in-office pad tests, and quality of life (QOL) questionnaires. The primary composite efficacy endpoint was the percentage of patients with ≥50% IEF reduction or ≥50% reduction in either pad test 12 months post-treatment. Patients were unblinded after completing 12-month visits, and patients who received placebo could opt to receive an open-label AMDC-USR treatment. Patients were followed for 2 years after initial treatment.

RESULTS: Overall, 143 patients were treated (50 placebo; 93 AMDC-USR), 141 patients completed 12-month visits (50 placebo, 91 AMDC-USR), 127 patients completed 2-year visits, and 3 patients remain in follow-up. Both placebo and AMDC-USR groups had similar baseline characteristics. No AMDC-USR safety signals were identified and no urinary retention was reported. Due to an unexpectedly high placebo responder rate with the composite endpoint, which included pad tests, enrollment was halted at 61% (150/246) of the planned study size. In post hoc analyses, IEF reduction correlated with QOL score improvement and suggested that ≥50% IEF reduction, ≥75% IEF reduction, and ≤1 leak per 3 days may be clinically meaningful endpoints. With these alternate endpoints, placebo rates were reduced and a potential treatment effect was detected (Figure). Further, 84% (37/44) of AMDC-USR patients with ≥50% IEF reduction at 12 months and available 2-year diaries also met this endpoint at 2 years. At final follow-up, 56% (20/36) of patients who received open-label AMDC-USR and had ≥3 stress leaks at 12 months had ≥50% IEF reduction compared to the 12-month diary collected before unblinding.

CONCLUSIONS: In women with SUI, AMDC-USR is safe and may provide durable reduction in IEF.



Source of Funding: Cook MyoSite, Incorporated

PNFBA-04

ASSOCIATION BETWEEN URINARY SYMPTOM SEVERITY AND AUTOMATED SEGMENTATION OF WHITE MATTER PLAQUE IN WOMEN WITH MULTIPLE SCLEROSIS

Siobhan Hartigan, Philadelphia, PA; Steven Weissbart, Stony Brook, NY; Michel Bilello, Diane Newman, Alan Wein, Ariana Smith, Philadelphia, PA*

INTRODUCTION AND OBJECTIVES: Multiple sclerosis (MS) is characterized by demyelinated white matter plaque throughout the central nervous system. Patients with MS frequently experience a range of bothersome urinary symptoms. The cingulate cortex, insula cortex, and prefrontal cortex are three cortical brain regions that regulate micturition, and plaque involvement in these regions may be associated with urinary symptom severity. The aim of this study is to investigate the relationship between cerebral plaque volume, location, and urinary symptoms in women with MS.

METHODS: We conducted a prospective case control study of women with MS undergoing routine yearly brain MRI. Women were administered the AUA Symptom Score (AUASS) and divided into two groups: women with severe urinary symptoms (AUASS ≥20) and women with mild symptoms (AUASS ≤7). MS plaque volume and location in the brain were determined using a validated automated white matter lesion segmentation algorithm. Mann Whitney U and Spearman's rank tests were used to investigate the relationship between plaque volume, location, and AUASS subscale scores.

RESULTS: The study included 36 women with a median age of 50.1 years (IQR 27.1) and BMI 26.6 kg/m2 (IQR 5.8) with no significant differences between groups, $p>0.05$. The median total plaque volume was 2523.5mm^3 (IQR 11705.5) and did not differ between the groups, $p=0.52$. Women with severe urinary symptoms had larger median plaque volume in the left frontal lobe (LFL) (623.5mm^3 IQR 2652 vs. 184mm^3 IQR 908; $p=0.04$) and right limbic lobe (RLL) (1.5mm^3 IQR 10 vs. 0 IQR 0; $p=0.02$) compared to women with mild urinary symptoms. Within the RLL, women with severe symptoms had larger median plaque volume in the cingulate gyrus (median 1 IQR 4 vs. median 0 IQR 0; $p=0.02$). There was moderate correlation between LFL lesion volume and the AUA voiding symptom subscore (coefficient 0.4, $p=0.03$) as well as RLL lesion volume and the AUA voiding symptom subscore (coefficient 0.5, $p=0.002$). However, these regions did not correlate with the storage subscore. There were no significant relationships between symptoms severity and plaque volume in the insula, cerebellum, corpus callosum, occipital or parietal lobes ($p>0.05$).

CONCLUSIONS: Urinary symptom severity in women with MS is associated with plaque in the cingulate gyrus and LFL, and not total cerebral plaque volume. The voiding symptom subscore of AUASS correlated with the volume of plaque in these locations. Further research to assess spinal cord plaque characteristics is underway.

Source of Funding: Funding provided by the National Institute of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant number P20 DK097819-01.

PNFBA-05

SPECIFIC CHANGES IN BRAIN ACTIVITY IN WOMEN WITH OVERACTIVE BLADDER AFTER SUCCESSFUL SACRAL NEUROMODULATION WITH INTERSTIM®: AN FMRI STUDY

Steven Weissbart, Stony Brook, NY; Rupal Bhavsar, John Detre, Hengyi Rao, Alan Wein, Lily Arya, Ariana Smith, Philadelphia, PA*

INTRODUCTION AND OBJECTIVES: Sacral neuromodulation (SNS) with InterStim® is efficacious for the treatment of overactive bladder (OAB); however, its mechanism of action is unclear, and there are no objective markers of response. Prior functional neuroimaging studies have suggested that women with OAB have increased brain activity in the cingulate cortex, insula, and frontal cortex, in response to bladder filling. The aim of this study was to investigate the effect of SNS on brain activity in women with OAB.

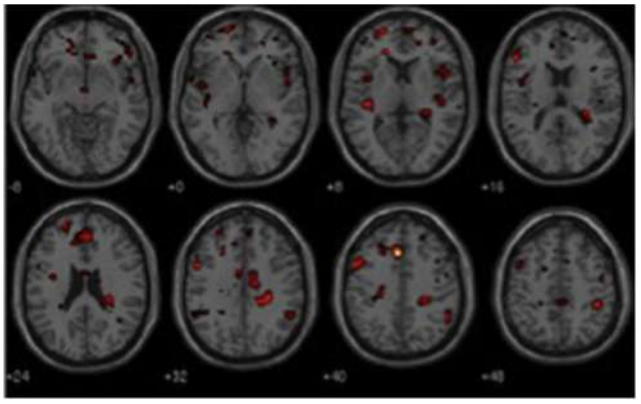
METHODS: We conducted a prospective mechanistic study of women with OAB (measured on validated questionnaire) undergoing InterStim®. Prior to stage 1 InterStim®, women underwent BOLD fMRI during bladder filling. During filling, women were asked to signal the experience of urgency. Women who completed stage 2 InterStim® underwent a 2nd BOLD fMRI during bladder filling 6 weeks after

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InterStim® implantation. Brain activity during urgency was compared to no urgency, and analysis was stratified according to response to InterStim®.

RESULTS: The study included 12 women with idiopathic OAB with normal emptying (median age 63.5, IQR 11 years). All women underwent pre-InterStim® fMRI, and 7 completed stage 2 InterStim® and underwent post-InterStim® fMRI (i.e. 7 responders, 5 non-responders). Among responders, brain activity decreased in the left cingulate gyrus (x,y,z coordinates: -5, 23, 39, $p=0.048$) and left frontal gyrus (-5, 23, 39, $p=0.04$) after InterStim® implantation (figure 1). There were no areas of increased brain activity after InterStim® implantation. Women who responded to InterStim® had increased brain activity on their pre-InterStim® fMRI in multiple cortical regions, including the cingulate cortex, inferior frontal gyrus, insula, and thalamus. There were no differences in ICIQ-FLUTS filling scores or pre-InterStim® fMRI filling volumes between responders and non-responders ($p>0.05$).

CONCLUSIONS: SNS with InterStim® appears to attenuate increased brain activity in women with OAB. Women with OAB and increased brain activity during bladder filling may experience greater treatment response. fMRI has preliminarily detected a phenotype of OAB that may predict therapeutic response to InterStim®.



Source of Funding: SUFU Neuromoduation Grant Award

Sexual Function/Dysfunction: Basic Research & Pathophysiology I

Moderated Poster 45

Sunday, May 14, 2017 **7:00 AM-9:00 AM**

MP45-01
POST-TRANSLATIONAL MODIFICATION OF NEURONAL NITRIC OXIDE SYNTHASE IN THE HUMAN ERECTILE TISSUE FOLLOWING RADICAL PROSTATECTOMY

Serkan Karakus, Biljana Musicki, Arthur L. Burnett, Baltimore, MD*

INTRODUCTION AND OBJECTIVES: Erectile dysfunction (ED) is a highly prevalent complication of radical prostatectomy (RP) with a reported incidence as high as 90%. Our previous studies in a rat model of bilateral cavernous nerve injury, which mimics nerve injury following RP, showed that neuronal nitric oxide synthase (nNOS) phosphorylation and uncoupling occurs in association with increased oxidative stress in the penis. However, the mechanisms of nNOS regulation in RP-associated ED in humans are poorly understood. We evaluated the effect of RP-associated cavernous nerve injury on nNOS post-translational modification in human erectile tissue.

METHODS: Human erectile tissue was obtained from 6 patients with RP-associated ED (median age: 60 [50-71] years) (53.5 months [22-117] after RP) and from 4 patients with non-ED Peyronie's disease (median age: 57.5 [53-59] years) as controls. RP group had severe ED (SHIM (The Sexual Health Inventory for Men) score=1 [1-2]) (preop RP SHIM score=22 [18-25]). Peyronie's disease patients in control group did not have ED based on SHIM score (SHIM $>$ 21) and penile doppler ultrasonography results. No patients in either group had comorbidities such as diabetes mellitus, hypertension, hypercholesterolemia or cardiovascular diseases. Samples were collected for molecular analyses of nNOS phosphorylation on activating (Ser-1412) and inhibitory (Ser-847) site, total nNOS expression, nNOS uncoupling (source of oxidative stress), caveolin-1 binding to nNOS (which decreases nNOS activity) and P-VASP Ser-239 (which indicates the integrity of nitric oxide signalling) by Western blot.

RESULTS: nNOS protein expression was decreased ($p<0.05$) in RP group compared to Control group. nNOS phosphorylation on positive (Ser-1412) regulatory site was decreased ($p<0.05$) while phosphorylation on negative (Ser-847) regulatory site was increased ($p<0.05$) in RP group compared to Control group. Caveolin-1 binding to nNOS was increased ($p<0.05$), while P-VASP (Ser-239) expression was decreased ($p<0.05$) in RP group compared to Control group. nNOS uncoupling was not different between groups.

CONCLUSIONS: nNOS function in the penis is impaired by deranged phosphorylation and increased binding Caveolin-1 to nNOS, conceivably resulting in ED in the face of RP. Our description of molecular factors contributing to the pathogenesis of RP-associated ED at the human level is relevant for advancing clinically therapeutic approaches to restore erectile function in RP patients.

Source of Funding: none

MP45-02
ALTERATIONS OF MICRORNA EXPRESSION IN A CAVERNOUS NERVE INJURY RAT MODEL

Chunhui Liu, Yanna Cao, Tien C Ko, Run Wang, Houston, TX*

INTRODUCTION AND OBJECTIVES: MicroRNAs (miRs) are noncoding, endogenous RNA molecules that regulate gene expression at the posttranscriptional level and play roles in various pathophysiological functions including erectile dysfunction (ED). The aim of this study was to identify miRs expressed in post-prostatectomy ED penis tissue and to analyze the target genes and signaling pathways regulated by the dysregulated miRs.

METHODS: RNA was isolated from the penis tissues from shame group and rats with cavernous nerve injury induced erectile dysfunction. The P1 chip from Thermo Fisher was used to analyse the miRNA expression profiling. The miRNA profilings were further validated by real-time polymerase chain reaction. The TargetScan and DAVID were used for bioinformatic analysis.

RESULTS: 124 miRNAs was found dysregulated in ED groups, in which 122 miRNAs were up-regulated. Of the 122 miRNAs, 21 miRNAs changed above twofold. miR-142, miR-101a and miR-200a were finally validated over-expressed in ED groups. TargetScan v7.1 was used to generate lists of target genes regulated by the two miRNAs. The lists were then sent to the bioinformatics database DAVID. GO and KEGG pathway analyses of the targets were performed. The results revealed that the three miRNAs could be involved in the processes of cell proliferation, differentiation, apoptosis, and so on. After bioinformatic analysis, Table 1 listed 4 pathways which correlated to the three miRNAs with statistical significance (P value $<$ 0.05), and also might be involved in the pathogenesis of ED.

CONCLUSIONS: Three miRNAs were found up-regulated significantly in the corpus cavernosum of rats with cavernous nerve injury induced ED. The three miRNAs might play important roles in the development of ED by regulating several of pathways but future studies are needed to validate these regulation mechanisms directly.

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