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INTRODUCTION AND OBJECTIVES: A conus medullaris syndrome results from an injury to the conus medullaris and cauda equine portions of the spinal cord. The clinical presentation is characterized by a lower motor neuron weakness affecting both skeletal muscles and pelvic organs with signs of paralysis, sensory disturbance and impairments of bladder, bowel, and sexual functions. The goal of the present study was to translate the unilateral lumbosacral ventral root avulsion (VRA) injury model from the rat to rhesus macaques, and to determine early and late effects of pelvic target denervation on lower urinary tract and external anal sphincter (EAS) function.

METHODS: A total of 6 female rhesus macaques were included. A unilateral L6-S3 VRA injury was performed and resulted in a lesion of all preganglionic parasympathetic fibers of the ipsilateral pelvic nerve and all somatic motor fibers of the ipsilateral pudendal nerve. Urodynamics and EAS electromyography (EMG) were performed under ketamine anesthesia in control subjects (n=6), and at 1 month and 6 months after the unilateral VRA injury (n=4).

RESULTS: The bladder infusion rate was between 85 and 120 mL/min to partially fill the bladder and induce reflux voiding. Poor voiding efficiency and compliance, and a slower urine flow rate were found in VRA tested subjects. The EAS guarding reflex was tested using a rectal probe. The maximum amplitude and area under the curve of EAS EMG were significantly decreased at 1 month after injury, but recovered at 6 months. Power spectrum (Fig. 1) showed that the peak frequency increased at 1 month after injury, but it was reduced to normal state at 6 month. The mean frequency was decreased at 1 and 6 months after injury.

CONCLUSIONS: This model eliminated the parasympathetic fibers of pelvic nerve and the somatic motor fibers of pudendal nerve, which resulted in detrusor underactivity and poor EAS contractility. Power spectrum analysis indicated that fewer motor units fired during EAS contraction after injury. This model in rhesus macaques mimics the clinical phenotype of conus medullaris syndrome using a lumbosacral VRA injury approach in long-term studies. It may provide a useful model to test the utility of emerging treatments after denervation of pelvic targets.

Source of Funding: none

MP85-04
DEVELOPMENT OF AN UNDERACTIVE SYNDROME OF PELVIC TARGETS IN LONG-TERM STUDIES AFTER A UNILATERAL AVULSION INJURY OF LUMBO SACRAL VENTRAL ROOTS IN RHESUS MACAQUES

Huiyi Harriet Chang*, Jih-Chao Yeh, Rebecca Do, Los Angeles, CA; Jaime H Nieto, Flushing, NY; Kari L Christe, Davis, CA; Leif A. Havton, Los Angeles, CA

INTRODUCTION AND OBJECTIVES: A conus medullaris syndrome results from an injury to the conus medullaris and cauda equine portions of the spinal cord. The clinical presentation is characterized by a lower motor neuron weakness affecting both skeletal muscles and pelvic organs with signs of paralysis, sensory disturbance and impairments of bladder, bowel, and sexual functions. The goal of the present study was to translate the unilateral lumbosacral ventral root avulsion (VRA) injury model from the rat to rhesus macaques, and to determine early and late effects of pelvic target denervation on lower urinary tract and external anal sphincter (EAS) function.

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Source of Funding: none

MP85-05
LONG-TERM FOLLOW-UP REVEALS DIFFERENTIAL PHENOTYPES OF NEUROLOGIC IMPAIRMENT AND BLADDER FUNCTION IN A MURINE MODEL OF NEURODEGENERATION

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INTRODUCTION AND OBJECTIVES: Patients with multiple sclerosis (MS) develop a variety of lower urinary tract (LUT) symptoms. We recently characterized a murine model of coronavirus-induced encephalomyelitis (CIE model), and confirmed that CIE mice develop neurogenic bladder dysfunction that was comparable with neurogenic LUTS observed in MS patients. Identified mechanisms were morphologic changes in the centers controlling micturition, spinal cord gliosis, and increased expression of pro-inflammatory cytokines. In the current study, we aimed to understand the long-term effects of neurodegenerative changes on micturition patterns and bladder physiology, as well as uncover the mechanisms of long-lasting neurogenic bladder dysfunction.

METHODS: Adult C57BL/6J mice were inoculated with 20 μl of mouse hepatitis virus (MHV, N=44, CIE mice) or PBS (N=19). Neurological symptoms and mouse weight were recorded daily, and voiding behavior weekly up to 8 wks pi. Neurologic symptoms were evaluated by the Clinical Symptoms Score (CSS) on a scale from 0 (asymptomatic) to 4 (quadripareis/paralysis). Detrusor contractility was evaluated in vitro at 10 wks. Based on CSS, CIE mice were assigned to 2 groups: recovery (REC group), and relapse (RELAP group). RELAP group was defined based on: (1) presence of symptom-free period at least for 24 hrs after initial rise in CSS, (2) presence of 2 symptom-free periods (24 h duration each), and (3) CSS>2 during the relapse.

RESULTS: Long-term follow up of CIE mice revealed two different neurological phenotypes: 1-recovery from initial acute neurologic impairment (REC, 73.5% of all CIE mice, N=25); and 2-relapse in symptoms (RELAP, 26.5% of all CIE mice, N=9). Eight percent of mice in REC group still had CSS≥2 at 8 wks in comparison to 22.2% in RELAP group. Animals in both REC and RELAP groups showed the most significant weight loss at 1wk. (22.3±0.28g at baseline vs 16.5±0.3g in REC group, and 9.2±0.86g in RELAP group, p<0.05). Isolated bladder strips from CIE mice did not have significant differences in muscarinic responses to EFS, however, RELAP group showed significantly decreased M3 responses along with increased micturition frequency at 5-6 wks.
CONCLUSIONS: Long-term follow up of CIE mice revealed two differential phenotypes of neurologic impairment mimicking two forms of MS in humans: relapsing-remitting MS and chronic inflammatory type of MS. Mice in RELAP group had a decreased response to M3 agonists suggesting that anti-muscarinic drugs may have limited effects on neurogenic bladder in this type of MS.

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MP85-06
BRAIN NETWORKS CONTROLLING BLADDER FILLING AND VOIDING
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INTRODUCTION AND OBJECTIVES: Lower urinary tract symptoms (LUTS) are common and poorly understood; treatment is often ineffective. Failure of neural control of bladder function likely contributes to LUTS symptoms in many patients. Prior studies have shown that the pontine micturition center (PMC) directly controls voiding. Within the PMC corticotropin releasing hormone neurons (PMCCRH) project axons directly to spinal sacral cord nuclei that control bladder contraction. Here we show that PMCCRH neurons are critical for voiding, project axons directly to spinal sacral cord nuclei that control bladder filling, and is a potential mechanism of LUTS in mouse models that should be translatable to human disease.

RESULTS: Stimulating PMCCRH neurons using designer receptors exclusively activated by designer drugs (DREADDs) produces urinary frequency in awake mice and on anesthetized CMG. Also, ablating PMCCRH neurons by selective expression of diphtheria toxin A receptors exclusively activated by designer drugs (DREADDs) produces voiding, in normal and disease states.

METHODS: We inject adeno-associated viruses expressing proteins in a Cre-dependent fashion into anatomically defined regions of mice expressing Cre recombinase in specific neural types, to cause highly selective expression of these probes in target neuron populations. We monitor conscious voiding with micturition video thermography (MVT), and CMG under anesthesia while monitoring/stimulating specific neuron groups.

RESULTS: Stimulating PMCCRH neurons using designer receptors exclusively activated by designer drugs (DREADDS) produces urinary frequency in awake mice and on anesthetized CMG. Also, ablating PMCCRH neurons by selective expression of diphtheria toxin A disrupts normal voiding and the normal CMG voiding reflex. To identify neurons which provide input to PMCCRH, we used modified rabies virus and cholera toxin B labeling of PMCCRH and confirmed our results with viral anterograde tracing. Afferents to PMCCRH are located in PAGVL, the preopercular area, the lateral hypothalamic area, and other sites. Because sacral afferents sensing bladder filling project to PAGVL, we determined the impact of stimulating Glutamatergic or GABAergic neurons (PAGGLUT or PAGGABA) in this region. Chemogenetic or optogenetic stimulation of PAGGLUT neurons leads to voiding and detrusor contraction. By contrast, chemogenetic or optogenetic activation of PAGGABA inhibits voiding and delays detrusor contraction on CMG.

CONCLUSIONS: 1. PMCCRH are driver neurons for detrusor contraction/voiding. 2. PAGGLUT project to PMCCRH and when firing drive voiding/detrusor contraction. 3. PAGGABA project to PMCCRH and inhibit voiding/detrusor contraction. PAGVL, which receives bladder-based sacral afferents, likely controls bladder filling, and is a potential target in efforts to control urge incontinence and urgency symptoms of LUTS.

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MP85-07
FUNCTIONAL NEUROIMAGING OF URINE STORAGE AND VOIDING IN MICE
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INTRODUCTION AND OBJECTIVES: Lower urinary tract symptoms (LUTS) are common and poorly understood; treatment is often ineffective. Failure of neural control of bladder function likely contributes to LUTS symptoms in many patients. Mice are continent and serve as excellent models of LUTS, in part because they can be manipulated genetically. To relate what is learned in mice to humans, we have developed functional MRI methods for mice which mirror those in humans. Such methods will allow us to compare directly the activation patterns of mouse and human brains during bladder filling and voiding, in normal and disease states.

METHODS: Mice are anesthetized with urethane and a catheter is implanted in the bladder dome. Blood Oxygen Level Detection Magnetic Resonance Imaging (BOLD-MRI) is carried out in a Bruker 9.4T magnet with a 4 element mouse brain phased array coil. A series of 2D multislice gradient echo-planar images are acquired every 2s, while the mouse undergoes cystometry. 25 slices are acquired with slices of 500μm, intensice distance 600μm and in-plane resolution of 250μm. Imaging occurs over a 45 minute time frame during which the mouse undergoes 10-15 voiding cycles (CMG). Data are analyzed with Statistical Parameter Mapping (SPM12) software using mouse brain adaptations. Linear modeling proceeds in 2 stages; first by providing a statistical map of the brain of individual animals and second by combining results across all animals in a group.

RESULTS: Preliminary results on female C57BL6/J (n =5) with a fixed effects analysis identified candidate regions across the brain with clear activation in the right Pontine Micturition Center (PMC) observed, which was confirmed by a region based random effects analysis. Negative contrast identified more extensive regions such as the periaqueductal gray and inferior colliculus with an indication that these regions are “switched off” during the transition to voiding.

CONCLUSIONS: Although technically challenging due to the small size, BOLD-MRI on mice is feasible and reveals regions of brain activation related to voiding cycles. Development of this technique along with fine mapping of brain circuits related to voiding will help define mechanisms of LUTS in mouse models that should be translatable to human disease.

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MP85-08
NON-SURGICAL MANAGEMENT OF DETRUSOR LEAK POINT PRESSURES ABOVE 40 CM H2O IN ADULTS WITH CONGENITAL NEUROGENIC BLADDER
Giulia Lane*, Ronak Gor, Minneapolis, MN; Jenna Katroski, St. Paul, MN; Sean Elliott, Minneapolis, MN

INTRODUCTION AND OBJECTIVES: Poorly compliant neurogenic bladders (NGB) with detrusor leak point pressures above 40 cm H2O (dLPP>40) have been associated with deterioration of renal function in children. As such, dLPP>40, despite clean intermittent catheterization (CIC) and anticholinergics, often mandates augmentation or diversion. While we recommend augmentation cystoplasty or diversion to appropriate patients, many elect for non-surgical management. Non-surgical management consists of rigorous urodynamic (UDS) and renal ultrasound (RUS) follow-up, paired with adjustments to CIC routine to keep bladder volumes below that volume at which dLPP>40, adjustments to anticholinergics, and intradetrusor botulinum toxin Type A (BTX). We describe the renal function outcomes of non-surgical management of adults with poorly compliant (dLPP>40) NGB.

METHODS: We retrospectively reviewed the charts of all patients at our Gillette Lifetime adult congenital urology clinic undergoing UDS from January 2011 to June 2016. Patients with dLPP>40 who opted for non-surgical management were included; this study was noted as their “index UDS” for calculation of follow-up. The primary endpoint was deterioration of renal function as evidenced by change in chronic kidney disease (CKD) stage, progression to CKD-III, or new/worsening hydrenephrosis.

RESULTS: Of 210 patients who underwent UDS, 45 had dLPP>40. After exclusions for incomplete data (n=7) or augmentation cystoplasty (n=11), 27 were the subject of study. 15/27 (56%) were women and all 27 were Caucasian. Median age was 29 years (IQR 25,